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(54) Title: **CROSSLINKING OF POLYETHYLENE FOR LOW WEAR USING RADIATION AND THERMAL TREATMENTS**

(57) Abstract

The present invention discloses methods for enhancing the wear-resistance of polymers, the resulting polymers, and *in vivo* implants made from such polymers. One aspect of this invention presents a method whereby a polymer is irradiated, preferably with gamma radiation, then thermally treated, such as by remelting or annealing. The resulting polymeric composition preferably has its most oxidized surface layer removed. Another aspect of the invention presents a general method for optimizing the wear resistance and desirable physical and/or chemical properties of a polymer by crosslinking and thermally treating it. The resulting polymeric composition is wear-resistant and may be fabricated into an *in vivo* implant.

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CROSSLINKING OF POLYETHYLENE FOR LOW WEAR
USING RADIATION AND THERMAL TREATMENTS

10 This application is based on U.S. provisional applications: serial number 60/017,852 filed on July 9, 1996; serial number 60/025,712 filed on September 10, 1996; and U.S. provisional application, "Crosslinking of Polyethylene for Low Wear Using Radiation and Thermal Treatments", of Fu-
15 Wen Shen et al., with attorney docket number 5910-108P3 (correct serial number not yet assigned), filed on April 29, 1997.

Technical Field Of The Invention

20 The present invention relates to polymers. It discloses methods for enhancing the wear-resistance of polymers by crosslinking and thermally treating them. The polymers disclosed herein are useful for making implants, for example, as components of artificial joints such as acetabular
25 cups.

Background Of The Invention

30 Ultrahigh molecular weight polyethylene (hereinafter referred to as "UHMWPE") is commonly used to make prosthetic joints such as artificial hip joints. In recent years, it has become increasingly apparent that tissue necrosis and interface osteolysis, in response to UHMWPE wear debris, are primary contributors to the long-term loosening failure of prosthetic joints. For example, wear of acetabular cups of UHMWPE in artificial hip joints introduces many microscopic
35 wear particles into the surrounding tissues. The reaction

to these particles includes inflammation and deterioration of the tissues, particularly the bone to which the prosthesis is anchored. Eventually, the prosthesis becomes painfully loose and must be replaced.

Improving the wear resistance of the UHMWPE socket and, thereby, reducing the rate of production of wear debris would extend the useful life of artificial joints and permit them to be used successfully in younger patients. Consequently, numerous modifications in physical properties of UHMWPE have been proposed to improve its wear resistance.

UHMWPE components are known to undergo a spontaneous, post-fabrication increase in crystallinity and changes in other physical properties. {See e.g., Rimnac, C.M., et al., J. Bone & Joint Surgery, 76-A(7):1052-1056 (1994)}. These changes occur even in stored (non-implanted) cups after sterilization with gamma radiation, which initiates an ongoing process of chain scission, crosslinking, and oxidation or peroxidation involving the free radicals formed by the irradiation. These degradative changes may be accelerated by oxidative attack from the joint fluid and cyclic stresses applied during use.

In an attempt to improve wear resistance, DePuy-DuPont Orthopaedics fabricated acetabular cups from conventionally extruded bar stock that previously had been subjected to heating and hydrostatic pressure that reduced fusion defects and increased the crystallinity, density, stiffness, hardness, yield strength, and increased the resistance to creep, oxidation and fatigue. Alternatively, silane cross-linked UHMWPE (XLP) has also been used to make acetabular cups for total hip replacements in goats. In this case, the number of *in vivo* debris particles appeared to be greater for XLP than conventional UHMWPE cup implants {Ferris, B.D., J. Exp. Path., 71:367-373 (1990)}.

Other modifications of UHMWPE have included: (a) reinforcement with carbon fibers; and (b) post-processing treat-

ments such as solid phase compression molding. Indeed, carbon fiber reinforced polyethylene and a heat-pressed polyethylene have shown relatively poor wear resistance when used as the tibial components of total knee prosthesis.

5 {See e.g., Rimmac, C.M., et al., Trans. Orthopaedic Research Society, 17:330 (1992)}.

Recently, several companies have modified the method of radiation sterilization to improve the wear resistance of 10 UHMWPE components. This has typically involved packaging the polyethylene cups either in an inert gas (e.g., Howmedica, Inc.), in a partial vacuum (e.g., Johnson & Johnson, Inc.) or with an oxygen scavenger (e.g., Sulzer Orthopaedics, Inc.).

15

Summary Of the Invention

The present invention comprises two aspects:

20 The first aspect of the invention presents a method for increasing the wear resistance of a polymer by crosslinking the polymer, followed by thermally treating the crosslinked polymer. Non-limiting examples of the thermal treatments are remelting or annealing. Preferably, the polymer is 25 crosslinked by gamma irradiation in the solid state prior to being modified to a desired final form or shape of the final product. In the preferred embodiment, the surface layer of the crosslinked and thermally treated polymer, which is the most oxidized and least crosslinked part of the polymer, is removed, e.g., in the process of machining the final product 30 out of the irradiated bar and thermally treated bar or block. The radiation dose is also preferably adjusted so that the optimal dose occurs within the solid polymer bar or block at the level of the bearing surface of the final product. Also presented are the polymers made from this 35 method; methods for making products (e.g., *in vivo* implants) from these polymers; and the products (e.g., *in vivo* implants) made from these polymers.

20 The second aspect of the invention provides a systematic method for determining an optimal balance among wear resistance and other physical and/or chemical properties that are deemed important to the long-term performance of an implant in vivo, and applying this optimal balance to determine the appropriate crosslinking and thermal treatment 25 conditions for processing a polymer. A flowchart is provided as a non-limiting illustration of the method for determining the optimal balance. Also provided are methods for treating polymers which apply the above appropriate crosslinking and thermal treatment conditions; the polymers produced by these 30 methods; methods for making products (e.g., in vivo implants) from these polymers; and the products (e.g., in vivo implants) made from these polymers.

Brief Description Of The Drawings

35 FIG. 1 presents the degree of crystallinity vs. depth at indicated doses for UHMWPE that was irradiated in a vacuum (i.e., a low-oxygen atmosphere).

40 FIG. 2 presents the gel content vs. depth at indicated doses for UHMWPE that was irradiated in a vacuum (i.e., a low-oxygen atmosphere).

FIG. 3 presents the gel content vs. depth at indicated conditions for UHMWPE.

FIG. 4 presents the degree of crystallinity vs. depth at indicated conditions for UHMWPE.

45 FIG. 5 presents the gel content vs. depth at indicated conditions for UHMWPE.

FIG. 6 presents the shape of the acetabular cup fabricated from the irradiated UHMWPE.

50 FIG. 7 presents a schematic diagram of the hip joint simulator used in the wear tests.

FIG. 8 presents the wear by volume loss of each cup of the four materials. Upper curves: 3.3 Mrad; Lower curves: 28 Mrad.

20 FIG. 9 presents the curves of the average volumetric wear and standard deviations of three cups of each material at each interval.

FIG. 10 presents the oxidation profile as a function of depth at various aging times.

25 FIG. 11 presents the oxidation profile as a function of depth at various aging times.

FIG. 12 presents the oxidation profile as a function of depth at various aging times.

30 FIG. 13 presents the oxidation profile as a function of depth at various aging times.

FIG. 14 presents the oxidation profile as a function of depth for various materials. The specimens were stored in air for 5 months and then aged for 20 days at 80°C.

FIG. 15 presents gel content as a function of depth at various aging times.

35 FIG. 16 presents gel content as a function of depth at various aging times.

FIG. 17 presents gel content as a function of depth at various aging times.

40 FIG. 18 presents gel content as a function of depth at various aging times.

FIG. 19 presents the degree of crystallinity as a function of depth after 30 days' aging.

Fig. 20 shows the combined soak-corrected wear for the non-aged and aged cups.

45 Fig. 21 shows the individual wear for cups irradiated at different doses.

Fig. 22 shows the average wear rate versus radiation dose of non-remelted and remelted cups.

50 Figs. 23A and 23B present the flowchart illustrating the optimization method of the present invention.

Fig. 24 graphically shows the oxidation profiles for irradiated and remelted UHMWPE as a function of depth from the UHMWPE bar surface.

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Fig. 25 graphically shows the tensile strength at yield versus radiation dose of irradiated UHMWPE with or without remelting, and non-irradiated and not remelted UHMWPE.

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Fig. 26 graphically shows the tensile strength at break versus radiation dose of irradiated UHMWPE with or without remelting, and non-irradiated and not remelted UHMWPE.

Fig. 27 graphically shows the elongation at break versus radiation dose of irradiated UHMWPE with or without remelting, and non-irradiated and not remelted UHMWPE.

30

Abbreviations used in this application are as follows:

UHMW -- ultra-high molecular weight

UHMWPE -- ultra-high molecular weight polyethylene

HMW -- high molecular weight

HMWPE -- high molecular weight polyethylene

35

The present invention contains two aspects. The first aspect of the invention provides methods for improving the wear resistance of a polymer by crosslinking (preferably the bearing surface of the polymer) and then thermally treating the polymer, and the resulting novel polymer. Preferably, the most oxidized surface of the polymer is also removed. Also presented are the methods for using the polymeric compositions for making products and the resulting products, e.g., *in vivo* implants. Specific examples of this method are presented in the section: "I. First Aspect of the Invention: Polymeric Compositions with Increased Wear Resistance" and "I (A) Further Examples of the First Aspect of the Invention", below.

50

The method of the invention utilizes irradiation for crosslinking a polymer followed by thermal treatment to decrease the free radicals to produce a preformed polymeric composition. The term "preformed polymeric composition" means that the polymeric composition is not in a final

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desired shape or form (i.e., not a final product). For
20 example, where the final product of the preformed polymeric
composition is an acetabular cup, irradiation and thermal
treatment of the polymer could be performed at pre-acetabu-
lar cup shape, such as when the preformed polymeric composi-
tion is in the form of a solid bar or block.

25 A second aspect of the invention provides a systematic
method (an example of which is illustrated in the flowchart,
below) for determining the optimal parameters for the above
mentioned crosslinking and thermal treatment. This second
30 aspect provides a method for determining the maximum possi-
ble improvement in wear resistance, consistent with keeping
the other physical and/or chemical propert(ies) within the
user's desired limits, with the least amount of trial and
error testing. Once the optimal parameters (i.e.,
35 crosslinking conditions such as radiation dose when radia-
tion is used to crosslink the polymer, and thermal treatment
parameters) are determined by this method, the polymer will
then be processed according to the optimal parameters. Thus,
this protocol renders the development of a preformed poly-
40 meric composition with particular chemical/mechanical char-
acteristics routine without resort to undue experimentation.
Also presented are the methods for using the preformed
polymeric composition for making products, and the products,
e.g., in vivo implants.

45 In the present invention, the wear resistance of the
polymer is improved by crosslinking. The crosslinking can
be achieved by various methods known in the art, for exam-
ple, by irradiation from a gamma radiation source or from an
electron beam, or by photocrosslinking. The preferred method
50 for crosslinking the polymer is by gamma irradiation. The
polymer is preferably crosslinked in the form of an extruded
bar or molded block.

In the preferred method, the crosslinked polymer is
subjected to thermal treatment such as by remelting (i.e.,

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heated above the melting temperature of the crosslinked polymer) or annealing (i.e., heated at below the melting temperature of the crosslinked polymer) to produce the preformed polymeric composition.

In the preferred embodiment of both the first and second aspects of the invention, the outer layer of the resulting preformed polymeric composition, which is generally the most oxidized and least crosslinked and, thus, least wear resistant, is removed. For example, the bearing surface of the preformed polymeric composition may be fashioned from inside, e.g., by machining away the surface of the irradiated and thermally treated composition before or during fashioning into the final product, e.g., into an implant. Bearing surfaces are surfaces which are in moving contact with another, e.g., in a sliding, pivoting, or rotating relationship to one another.

35

Choices of Polymers

The polymers are generally polyester, poly(methylmethacrylate), nylon, polycarbonates, and polyhydrocarbons such as polyethylene, and polypropylene. High molecular weight (HMW) and ultra-high molecular weight (UHMW) polymers are preferred, such as HMW polyethylene (HMWPE), UHMW polyethylene (UHMWPE), and UHMW polypropylene. HMW polymers have molecular weights ranging from about 10^5 grams per mole to just below 10^6 . UHMW polymers have molecular weights equal to or higher than 10^6 grams per mole, preferably from 10^6 to about 10^7 . The polymers are generally between about 400,000 grams per mole to about 10,000,000 and are preferably polyolefinic materials.

For implants, the preferred polymers are those that are wear resistant and have exceptional chemical resistance. UHMWPE is the most preferred polymer as it is known for these properties and is currently widely used to make acetabular cups for total hip prostheses and components of

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other joint replacements. Examples of UHMWPE are those
20 having molecular weight ranging from about 1 to 8×10^6 grams per mole, examples of which are: GUR 4150 or 4050 (Hoechst-Celanese Corporation, League City, Texas) with a weight average molecular weight of 5 to 6×10^6 grams per mole; GUR 4130 with a weight average molecular weight of 3 to 4×10^6 ; GUR 4120 or 4020 with a weight average molecular weight of 3 to 4×10^6 ; RCH 1000 (Hoechst-Celanese Corp.) with a weight average of molecular weight of 4×10^6 and HiFax 1900 of 2 to 4×10^6 (HiMont, Elkton, Maryland). Historically, companies which make implants have used
30 polyethylenes such as HIFAX 1900, GUR 4020, GUR 4120 and GUR 4150 for making acetabular cups.

Sterilization Methods

All polymeric products must be sterilized by a suitable method prior to implanting in the human body. For the formed crosslinked and thermally treated polymeric compositions (i.e., the final products) of the present invention, it is preferable that the products be sterilized by a non-radiation based method, such as ethylene oxide or gas plasma, in order not to induce additional crosslinking and/or oxidation of the previously treated preformed polymeric composition. Compared to radiation sterilization, a non-radiation sterilization method has a minor effect on the other important physical characteristics of the product.

45 Nevertheless, the method can be used in conjunction with radiation sterilization. If the final products are to be sterilized by an additional dose of radiation, it is preferable to take into account the effect of this additional radiation dose on the wear resistance and other properties of the polymer, in determining the optimum radiation dose used in the initial crosslinking. Furthermore, it is preferable that the radiation sterilization be done while
50 the final product (e.g., *in vivo* implant) is packed in a

20 suitable low-oxygen atmosphere (e.g., in partial vacuum, in an inert gas such as nitrogen, or with an oxygen scavenger included) in order to minimize oxidation of the surface layer of the final product during and after sterilization by irradiation.

25 The dose ranges in this application do not take into account radiation sterilization. If radiation sterilization is used, then the dose ranges may have to be adjusted. Such adjustment can be easily performed using the teachings herein. For example, if after comparing the dose-response curves for wear with those for other important physical or 30 chemical properties, it is determined that the optimal total radiation dose is 8 Mrad, and it is intended to sterilize the polymer with 2.5 Mrad gamma radiation (the minimum industrial standard sterilization dose), then the initial radiation dose (before sterilization) should be 5.5 Mrad, 35 such that the total dose (initial plus sterilization doses) will be 8 Mrad. These calculations are approximate, since the total crosslinking achieved will not be exactly equivalent to a single 8 Mrad dose.

40 Nevertheless, the applicants have discovered that a high level of crosslinking in the surface layer of a polymer markedly reduces the degradative effects of surface oxidation, i.e., that would otherwise occur if a non-pre-crosslinked polymer were irradiated in the presence of oxygen (for example, see Fig. 3).

45

Methods for Characterizing the Polymers

50 The degree of crystallinity can be determined using methods known in the art, e.g. by differential scanning calorimetry (DSC), which is generally used to assess the crystallinity and melting behavior of a polymer. Wang, X. & Salovey, R., J. App. Polymer Sci., 34:593-599 (1987).

Wide-angle X-ray scattering from the resulting polymer can also be used to further confirm the degree of

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20 crystallinity of the polymer, e.g. as described in Spruiell, J.E., & Clark, E.S., in "Methods of Experimental-Physics", L. Marton & C. Marton, Eds., Vol. 16, Part B, Academic Press, New York (1980). Other methods for determining the degree of crystallinity of the resulting polymer may include Fourier Transform Infared Spectroscopy {Painter, P.C. et al., "The Theory Of Vibrational Spectroscopy And Its Application To Polymeric Materials", John Wiley and Sons, New York, U.S.A. (1982)} and density measurement (ASTM D1505-68). Measurements of the gel content and swelling are generally used to characterize crosslink distributions in polymers, the procedure is described in Ding, Z.Y., et al., J. Polymer Sci., Polymer Chem., 29:1035-38 (1990). FTIR can also be used to assess the depth profiles of oxidation as well as other chemical changes such as unsaturation (Nagy, E.V., & Li, S., "A Fourier transform infrared technique for the evaluation of polyethylene orthopaedic bearing materials", Trans. Soc. for Biomaterials, 13:109 (1990); Shinde, A. & Salovey, R., J. Polymer Sci., Polym. Phys. Ed., 23:1681-1689 (1985)}.

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40 Use of Crosslinked Polymers for Implants

45 Another aspect of the invention presents a process for making implants using the preformed polymeric composition of the present invention. The preformed polymeric composition may be shaped, e.g., machined, into the appropriate implants using methods known in the art. Preferably, the shaping process, such as machining, removes the oxidized surface of the composition.

50 Preformed Polymeric Compositions

55 The preformed polymeric compositions of the present invention can be used in any situation where a polymer, especially UHMWPE, is called for, but especially in situations where high wear resistance is desired. More particu-

larly, these preformed polymeric compositions are useful for
20 making implants.

Implants Made of Crosslinked Polymers

An important aspect of this invention presents implants
that are made with the above preformed polymeric composi-
25 tions or according to the methods presented herein. In
particular, the implants are produced from preformed poly-
meric composition are UHMW polymers crosslinked by gamma
radiation followed by remelting or annealing, removing the
30 oxidized surface layer and then fabricating into a final
shape. The preformed polymeric composition of the present
invention can be used to make implants for various parts of
the body, such as components of a joint in the body. For
example, in the hip joints, the preformed polymeric composi-
35 tion can be used to make the acetabular cup, or the insert
or liner of the cup, or trunnion bearings (e.g. between the
modular head and the stem). In the knee joint, the pre-
formed polymeric composition can be used to make the tibial
plateau (femoro-tibial articulation), the patellar button
40 (patello-femoral articulation), and trunnion or other bear-
ing components, depending on the design of the artificial
knee joint. In the ankle joint, the preformed polymeric
composition can be used to make the talar surface (tibio-
talar articulation) and other bearing components. In the
elbow joint, the preformed polymeric composition can be used
45 to make the radio-numeral joint, ulno-humeral joint, and
other bearing components. In the shoulder joint, the pre-
formed polymeric composition can be used to make the
glenoro-humeral articulation, and other bearing components.
In the spine, the preformed polymeric composition can be
50 used to make intervertebral disk replacement and facet joint
replacement. The preformed polymeric composition can also
be made into temporo-mandibular joint (jaw) and finger

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20 joints. The above are by way of example, and are not meant to be limiting.

The following discusses the first and second aspects of the invention in more detail.

25 I. First Aspect of the Invention: Polymeric Compositions with Increased Wear Resistance

30 The first aspect of the invention provides preformed polymeric compositions which are wear resistant and useful for making *in vivo* implants. In this aspect, for polymers in general, and more preferably UHMW and HMW polymers, and most preferably UHMWPE and HMWPE, the irradiation dose is 35 preferably from about 1 to about 100 Mrad, and more preferably, from about 5 to about 25 Mrad, and most preferably from about 5 to about 10 Mrad. This most preferable range is based on achieving what the inventors have determined to be a reasonable balance between improved wear resistance and minimal degradation of other important physical properties.

40 *In vivo* implants of the present invention, i.e., irradiated within the above dose ranges are expected to function in *vivo* without mechanical failure. The UHMWPE acetabular cups used by Oonishi et al. [in Radiat. Phys. Chem., 39: 45 495-504 (1992)] were irradiated to 100 Mrad and functioned in *vivo* without reported mechanical failure after as long as 26 years of clinical use. Furthermore, it is surprising that, as shown in the EXAMPLES, acetabular cups from the preformed polymeric composition prepared according to the present invention, but irradiated to much less than 100 Mrad, exhibited much higher wear resistance than reported by Oonishi et al.

50 On the other hand, if a user is primarily concerned with reducing wear, and other physical properties are of secondary concern, then a higher dose than the above stipulated most preferable range (e.g., 5 to 10 Mrad) may be

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20 appropriate, or vice versa (as illustrated in the detailed examples in the following section). The optimum radiation dose is preferably based on the dose received at the level of the bearing surface in the final product. Gamma radiation is preferred.

25 The irradiated polymer is then preferably remelted at or above melting temperature of the irradiated polymer, e.g., in air. As used herein, the melting temperature of the crosslinked or irradiated polymer is identified from the peak of the melting endotherm as measured by DSC. Preferably, the remelting temperature is from about the melting 30 temperature of the irradiated polymer to about 100°C to about 160°C above the melting temperature of the irradiated polymer; more preferably from about 40°C to about 80°C above the melting temperature of the irradiated polymer; and most preferably from about 1°C to about 60°C above the melting 35 temperature of the irradiated polymer. For example, in the case of UHMWPE, the remelting temperature is preferably from about 136°C to about 300°C, more preferably from about 136°C to about 250°C, and most preferably from about 136°C to about 200°C. Specific conditions for remelting are described 40 in EXAMPLES 1 and 2, below.

45 Generally, in practice, the remelting temperature is inversely proportional to the remelting period. The polymer is preferably remelted over a period from about 1 hour to about 2 days, more preferably from about 1 hour to about 1 day, and most preferably from about 2 hours to about 12 hours.

50 Since, depending on the time and temperature applied, annealing can produce less of an effect than remelting on physical properties such as crystallinity, yield strength, and ultimate strength, annealing may be used in place of remelting as a means for reducing the free radicals remaining in the polymer after irradiation crosslinking, in order to maintain these physical properties within limits required

20 by the user. Thermal treatment, such as remelting or annealing, removes free radicals and thereby improves long term wear resistance of the polymer. On the other hand, annealing is slower and thus takes longer than remelting, making it likely to be more expensive in industrial applications.

25 The annealing temperature is preferably from about room temperature to below the melting temperature of the irradiated polymer; more preferably from about 90°C to about 1°C below the melting temperature of the irradiated polymer; and most preferably from about 60°C to about 1°C below the melting temperature of the irradiated polymer. For example, 30 UHMWPE may be annealed at a temperature from about 25°C to about 135°C, preferably from about 50°C to about 135°C, and more preferably from about 80°C to about 135°C. The annealing period is preferably from about 2 hours to about 7 days, and more preferably from about 7 hours to about 5 days, and most preferably from about 10 hours to about 2 days.

35 Instead of using the above range of radiation dose as a criterion, the appropriate amount of crosslinking may be determined based on the degree of swelling, gel content, or molecular weight between crosslinks after thermal treatment. 40 This alternative is based on the applicant's findings (detailed below) that acetabular cups made from UHMWPE falling within a preferred range of these physical parameters have reduced or non-detectable wear. The ranges of these physical parameters include one or more of the following: a degree of swelling of between about 1.7 to about 5.3; molecular weight between crosslinks of between about 400 to about 8400 g/mol; 45 and a gel content of between about 95% to about 99%. A preferred polymer or final product has one or more, and preferably all, of the above characteristics. These parameters can also be used as starting points in the second 50 aspect of the invention (as illustrated by the flowchart, discussed below) for determining the desired radiation dose to balance the improvement in wear resistance with other

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desired physical or chemical properties, such as polymer strength or stiffness.

25

After crosslinking and thermal treatment, preferably, the most oxidized surface of the preformed polymeric composition is removed. The depth profiles of oxidation of the preformed polymeric composition can be determined by methods known in the art, such as FTIR, described above and in EXAMPLES 3 and 6. In general, to remove the most oxidized surface, preferably a minimum of about 0.5 mm to 1.0 mm of the surface of preformed polymeric composition which is exposed to air is removed, e.g. by machining, before or while fashioning the preformed polymeric composition into the final product.

I. (A) Further Examples of the First Aspect of the Invention

35

As noted above, the most preferable range of dose for crosslinking radiation (i.e., from 5 to 10 Mrad) was based on achieving what the inventors have determined to be a reasonable balance between improved wear resistance and minimal degradation of other important physical properties. The following examples illustrate applications of the present invention with alternative criteria for the optimal dose. These examples use *in vivo* implants as non-limiting examples of the products, and UHMWPE or HMWPE bar or block as a non-limiting example of a starting material.

40

In the first example, the user desires to achieve a minimum wear rate of the *in vivo* implant made from the UHMWPE and HMWPE, and the other physical or chemical properties are important but of lesser concern. In such a case, the user may choose to irradiate the UHMWPE and HMWPE bar or block between about 15 Mrad to about 20 Mrad (as shown by Fig. 22). As discussed in the section "II(b) Application of the Flowchart", below, GUR 4150 is representative of UHMWPE and HMWPE. The irradiated UHMWPE or HMWPE bar or block is further remelted or annealed at a temperature and time

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described in "I. First Aspect of the Invention: Polymeric Compositions with Increased Wear Resistance", above.

20 In a second example, the user may wish to produce an UHMWPE which is as wear resistant as possible while meeting the tensile strength at break (ultimate), tensile strength at yield, and elongation at break criteria of the standard specified by the American Society for Testing and Materials 25 F-648 standard (hereinafter referred to as "ASTM F648") for UHMWPE for in vivo use. The information about this standard can be found in a current issue of the Annual Book of ASTM Standards, Medical Devices and Services, "Standard Specification for Ultra-High-Molecular-Weight Polyethylene Powder and Fabricated Form for Surgical Implants", American Society 30 for Testing and Materials. The method of the second aspect of the present invention (as illustrated by the flowchart) may be used to adjust the crosslinking and thermal treatment 35 parameters to meet any current ASTM F648 criteria.

For example, to meet the 1996 ASTM F648 (F648-96) criteria for Type 1 or 2 UHMWPE, the UHMWPE must have: a tensile strength at break (ultimate) of at least 35 MPa (for Type 1) and 27 MPa (for Type 2) at 23°C and 5.08 cm/min; a tensile strength at yield of at least 21 MPa (Type 1) and 19 40 MPa (for Type 2) at 23°C, and 5.08 cm/min; and elongation at break of at least 300% at 5.08 cm/min. The test conditions are described in ASTM D638, Type IV (Annual Book of ASTM Standards, American Society for Testing and Materials).

45 Alternatively, to meet the 1996 ASTM F648 criteria for Type 3 UHMWPE, the UHMWPE must have: a tensile strength at break (ultimate) of at least 27 MPa at 23°C and 5.08 cm/min; a tensile strength at yield of at least 19 MPa at 23°C, and 5.08 cm/min; and elongation at break of at least 250% at 50 5.08 cm/min.

The plots of mechanical properties vs irradiation dose for GUR 4150 (which is representative of Type 2 UHMWPE) (Figs. 25-27) show that, for all of the radiation

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20 doses between 5 to 25 Mrad, the above ASTM F648 criteria for
Types 2 UHMWPE are fulfilled except for the elongation at
break, which crosses the 300 limit at about 6 Mrad. Thus, if
the ASTM F648 criteria are to be met for Types 2 UHMWPE, the
maximum (i.e., the most preferred) gamma radiation dose is
about 6 Mrad. As illustrated in the second aspect of the
invention (following section), the corresponding curves of
25 wear and other physical properties vs. crosslinking dose
could be used to determine the preferred dose range for
other Types of UHMWPE or for other polymers in general.

30 II. Second Aspect of the Invention: Method for Optimizing
Wear Resistance and Desirable Physical and/or Chemical
Characteristics of a Polymeric Composition

35 The second aspect of the invention uses the findings in
this patent application (including those presented in the
"EXAMPLES" section, below) to construct a method which
allows one skilled in the art, to systematically identify
the conditions necessary to routinely produce a polymer with
40 an optimal balance of wear resistance and physical and/or
chemical properties, with minimal additional testing and
minimal trial and error. In one embodiment of this aspect
of the invention, the optimizing method can be schematically
illustrated in a flowchart. Once the optimal conditions have
45 been determined by this method, the polymer can then be
subjected to these conditions for processing.

50 The present invention is based in part, on the discovery that wear rate decreases with increasing radiation dose, and there is a maximum dose above which there is little or no additional improvement in wear, but higher doses might degrade other important physical and/or chemical properties of the polymer, such as yield or ultimate strength, elongation to failure, impact strength or fatigue resistance, as well as increasing the susceptibility to oxidation. Oxida-

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tion, in turn, is known to adversely affect one or more of these physical properties, and was shown to occur in the examples below for UHMWPE crosslinked at a dose averaging about 28 Mrad if there had been no thermal treatment. Consequently, a polymer irradiated at a high radiation dose may exhibit improved wear resistance, but its other physical or chemical properties may fall outside of desirable or allowable limits, such as those specified by ASTM F648 for UHMWPE for *in vivo* use.

The method is also based in part on the discovery that, while other important physical properties (such as crystallinity or elongation to break) may be markedly affected by the amount of thermal treatment (e.g., remelting or annealing) applied to the polymer after irradiation crosslinking, the wear resistance is not markedly affected. This latter discovery permits reducing the amount of additional testing required by the user in order to identify the crosslinking dose which will provide the user's desired balance among wear resistance and other physical properties. This method is useful, e.g., in the case where performed polymeric composition made of UHMWPE is used for making *in vivo* implants, such as acetabular cups.

II (a) Summary of the Steps of the Optimization Method

Thus, the second aspect of the present invention provides a systematic method for optimizing the balance among wear resistance and other desired physical and/or chemical characteristics of a polymer. The steps in this method are summarized in the non-limiting example of the flowchart of Figs. 23A and 23B. In the flowchart and the following discussion, for ease of discussion, irradiation is used as an example of a crosslinking method, and implant is used as an example of the product that is made from the polymer. However, as discussed elsewhere in this application, other crosslinking methods and products may be used.

20 Step 1: The process typically begins with the polymer in solid form, such as an extruded bar or block.

25 Step 2: The bar is irradiated over a range of doses up to the maximum that is likely to produce a material with the desired wear resistance and physical and/or chemical properties. This irradiation may be done, for example, in the case of gamma radiation by means of a cobalt 60 gamma radiation facility as is presently used for industrial-scale sterilization of implants.

30 Step 3: The irradiated bars are then remelted.

35 Applicants found that remelting of an irradiated polymer would substantially reduce the free radicals produced during irradiation, thus minimizing long-term oxidation and chain scission. By improving the polymeric composition's resistance to long-term oxidation, remelting also improves the polymeric composition's long-term resistance to wear. For further discussion of the subject, see EXAMPLES 2, 3, and 4, below

40 Although the bar may be contained in a low-oxygen atmosphere during the remelting, this may not be essential since, even if the bar is remelted in ambient air, the resultant oxidation may affect only the surface layer of the polymer (e.g. in the following EXAMPLE section, Figs. 2, 5, and 24, show oxidation extending to about 1 mm deep). In the preferred embodiment of the invention, the oxidized surface layer of the preformed polymeric composition will be removed, e.g., during subsequent machining of the products out of the treated bar.

45 Step 4A The radiation dose is correlated with the wear resistance of the products made from the irradiated remelted polymeric composition, as determined in a wear test that

adequately simulates the wear conditions of the products.
20 For example, if the polymeric composition will be made into an implant, then the wear test should preferably adequately simulate the wear conditions of such implants *in vivo*. The correlation may be arrived at by plotting a dose-response curve for irradiation dose vs. wear.

25 Step 4B: Similarly, the radiation dose is correlated with each of the physical and/or chemical properties that may be markedly affected by the radiation dose and that might, in turn, substantially affect the performance of the implant *in vivo*, both for non-remelted and remelted polymer. Again, 30 the correlation may be arrived at by plotting a dose-response curve for irradiation dose vs. each of these physical and/or chemical properties.

35 The user does not have to do dose vs. properties for each property that might be affected, but only those properties that are considered important for the proper functioning of the implant *in vivo*. Which of these properties are important for the intended application, and the limiting values of these properties, may vary for different polymeric 40 compositions and for different types of applications (e.g., hip prostheses compared to knee prostheses) and must, therefore, be established by the user before applying the flowchart.

45 Step 5 is the first attempt at optimization. The user may first decide on the desired amount of improvement in the wear resistance, i.e., the maximum wear rate that is permissible for the user's application. The dose-response curve for wear (Step 4A) then shows the minimum radiation dose 50 necessary to provide this amount of improvement in wear resistance.

Similarly, the dose response curves for the other physical or chemical properties deemed critical or important

20 (Step 4B) provide the values of these properties correspond-
ing to the specific radiation dose identified in Step 4A as
being necessary to provide the desired improvement in wear
resistance. If each of these other physical or chemical
25 properties are within allowable limits for the crosslinked
and remelted polymer, then an optimal method has been iden-
tified (Step 6). In other words, the implant can be made by
irradiating the solid polymer bar, remelting the bar and
machining out the implant; the entire process being con-
ducted such that the resulting implant has received the
optimal dose at its bearing surface.

30 Alternatively, the user may first decide on critical
values for one or more properties, such as ultimate tensile
strength, fatigue strength, etc., and then check the corre-
sponding dose response curves for the remelted polymer for
the maximum allowable dose, and then check the wear vs. dose
35 curve to determine whether this dose gives sufficient im-
provement in wear (i.e., the user does not necessarily have
to begin by choosing the desired amount of improvement in
wear).

40 However, if not enough improvement in wear will be
obtained while keeping these other chemical and physical
properties within allowable limits, or conversely, if the
dose required for the desired wear improvement causes one or
45 more of these properties to be out of allowable limits, then
the user can use a lower radiation dose (i.e., accept a
higher wear rate) if he wishes to remelt the materials or,
alternatively, annealing may be substituted for remelting
(Step 7). For a crosslinked material, annealing is less
efficient than remelting in removing free radicals, but may
cause less of a reduction in other important physical prop-
50 erties.

Whether annealing is a practical option will be appar-
ent from the dose-response curves for the non-remelted and

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20 remelted polymers. That is, if the desired value of the property in question falls between the two curves (see for example, Figs. 25 and 26), then a polymer with the desired limiting value may be produced by an annealing process with an appropriate time/temperature combination.

25 It is not necessary to generate additional wear dose-response curves for each of the many possible combinations of annealing time and temperature. It is expected that the radiation dose necessary to produce the desired reduction in wear that is determined from the wear dose-response curve for remelted polymer in Step 4A, will also apply to an 30 annealed polymer produced in Step 7.

35 Step 7: Anneal samples of a bar or block which have been irradiated to that dose that was identified in Step 4A as being necessary to provide the required improvement in wear resistance, at various time/temperature combinations, to produce a polymer with the critical properties between those for non-remelted and remelted materials.

40 Step 8: The physical or chemical propert(ies) of interest of the irradiated and annealed samples of the polymer are correlated with annealing times and temperatures.

45 Step 9: Using ultimate tensile strength as an example of the physical characteristic of interest, depending on the resultant curve for annealing time and/or temperature vs. ultimate strength, the radiation dose required to achieve the desired wear resistance identified in Step 4A (above) should produce a polymer with an ultimate strength within allowable limits.

50 Similar consideration should be given to each of the other important physical and/or chemical properties by generation of individual curves of these properties versus annealing time and/or temperature. If each of these proper-

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ties is within allowable limits at a particular annealing time and temperature combination, then a suitable method has 20 been identified (Step 10).

If an annealing process cannot be identified that maintains the properties within allowable limits, then the user may choose to accept a lower radiation dose (Step 11), 25 i.e., to accept less of an improvement in wear resistance. However, if a lower radiation dose (and, therefore, a greater wear rate) is acceptable, then the corresponding physical and chemical properties should again be checked for 30 the remelted polymer (using the correlation arrived earlier in Step 4B), since these may be within limits at the lower radiation dose.

If the properties are within limits for the remelted polymer at the lower radiation dose, then remelting may be used instead of annealing to produce a polymer with the desired improvement in wear resistance (Step 6). If not, 35 then the user should proceed with annealing as before (Steps 7 through 10 or 11) but at this lower radiation dose.

The user may wish to progressively reduce the required 40 amount of radiation crosslinking (i.e., to accept still higher wear rate) until a dose is identified for which all of the other properties deemed essential are within the user's required limits. The resultant dose represents the maximum improvement in wear resistance obtainable within the user's criteria.

45

II (b) Example Applications of the Flowchart

As starting points for the flowchart, the ranges for 50 radiation doses, remelting and annealing temperatures and times described in section "I. First Aspect of the Invention: Polymeric Compositions with Increased Wear Resistance" and "I (A) Further Examples of the First Aspect of the Invention", above, can be used, with regard to poly-

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mers in general, UHMW and HMW polymers in particular, and
20 HMWPE and UHMWPE especially.

For ease of discussion, the following examples illustrate the application of the flowchart using UHMWPE (which also behaves similar to HMWPE) as an example of a polymer and an acetabular cup as an example of an implant. GUR 4150 is representative of such a class of UHMWPE. Similarly, the 25 description uses gamma radiation as an example for crosslinking the polymer. These examples are meant to illustrate and not meant to limit the invention.

The method described by the flowchart is applicable to 30 other polymers, implants or other products made from such polymers, and crosslinking methods (examples of which are described elsewhere in this application), and methods for making an implant or product out of the preformed polymeric composition.

35 From the data provided by the EXAMPLES (following sections) a number of generalities were discovered that allowed simplification of the use of the flowchart, i.e., to minimize the amount of additional testing that would be required of a user wishing to apply the method to other 40 polymers, or to the GUR4150 of the EXAMPLES but with various optimization criteria.

To establish the critical curve for the reduced *in vivo* wear (Step 4A), the UHMWPE bar or block is preferably irradiated in Step 2 and remelted in Step 3, in a manner and to 45 a dose and temperature and time as described for UHMWPE in the section, "I. First Aspect of the Invention: Polymeric Compositions with Increased Wear Resistance" and "I (A) Further Examples of the First Aspect of the Invention", above.

50 In step 4A, acetabular cups are machined out of the irradiated bar and wear tested under conditions suitably representative of the intended *in vivo* application (e.g., by the method described in the EXAMPLES section below) to

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20 establish a wear vs. radiation dose response curve for the specific polymer. EXAMPLE 5 and Fig 22 show a wear dose-response curve for gamma irradiated GUR 4150 UHMWPE.

25 Applicants discovered that it is not necessary to generate additional wear dose-response curves for each of the many possible combinations of annealing time and temperature. This follows from the results of EXAMPLE 2. Since annealing is done at a lower temperature than remelting and, therefore, has a less marked effect on physical properties in general, it can be expected that annealing will have even less of an effect on the wear resistance than remelting.

30 Another important aspect of the invention is the discovery that wear resistance of GUR 4150 was not markedly affected by remelting and, therefore, it is also not likely to be markedly affected by annealing time and temperature. Therefore, it is expected that the radiation dose necessary 35 to produce the desired reduction in wear that is determined from the wear dose-response curve for remelted polymer in Step 4A, will also apply to an annealed polymer produced in Step 7. Therfore, while the user needs to do his own tests to establish tensile strength vs dose etc., he can rely on 40 the wear vs dose curve developed for the remelted material, rather than running an additional set of wear curves for each annealing condition. This represents a considerable saving in experimental costs, since the tensile strength tests typically may be completed in a few days (using common 45 tensile test apparatus), but the tests of wear vs dose require months to complete (and require highly specialized equipment and techniques available on only a handful of laboratories in the world).

50 Furthermore, if the user is working with GUR 4150, he can use the dose vs wear curve of Fig. 22 (as well as the plots of other mechanical properties, Figs. 25-27) without needing to run any wear or tensile tests. Finally, if he is working with another grade of UHMW polyethylene, he can

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20 probably use Fig. 22, since other tests have shown that the wear resistances of these materials are very similar to GUR 4150 for a given sterilization treatment. At the least, Fig. 22 establishes the range on which the user may focus his wear vs. dose experiments for other grades of UHMW polyethylene, to minimize the testing necessary to identify 25 the optimum dose.

For other polymers, comparable wear tests at each end of the range of interest for radiation dose could be applied to verify whether remelting or annealing also does not markedly affect their wear resistance. Nevertheless, GUR 30 4150 is representative of UHMWPEs, especially those useful for implants, in its physical and chemical properties, and applicants have observed that other UHMWPEs, of different molecular weights and with or without calcium stearate, such as GUR 1020 (calcium stearate free, lower molecular weight grade) behaved similarly to GUR 4150 in their wear resistance after irradiation sterilization in air. McKellop, H. et al., Trans. Society for Biomaterials, Vol. 20, pg. 43 (1997).

40 Further, it has been observed that, although the starting physical properties of HMWPE are different from those of UHMWPE, these differences will be substantially reduced after sufficient crosslinking. For example, they are almost equal after electron beam irradiation treatment to 300 kGy (30 Mrad), for properties like gel content, swelling and 45 strength. Streicher, R. M., Beta-Gamma 1/89: 34-43, at p. 42, right col., fourth full paragraph. Even the wear properties were the same, after the differences in the molecular arrangement between HMWPE and UHMWPE were offset by the irradiation procedure. Thus, it is predicted that the findings based on GUR 4150 and the above discussion would be 50 applicable to polymers in general, and to UHMW and HMW polymers, in particular, and especially HMWPE and UHMPE. Thus, the radiation, remelting and annealing ranges found

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20 for GUR 4150 can be applied to polymers in general, and more preferably to HMW and UHMW polymers, and most preferably to HMWPE and UHMWPE; and these ranges can be used at the very least, as starting points in the flowchart for determining the specific ranges for other polymers, and the data in the "EXAMPLES" section below will facilitate the user in arriving at the proper conditions for GUR 4150, ASTM F648 Type 2 25 UHMWPE, and UHMWPE and HMWPE in general.

30 The following examples illustrate the use of these generalities in conjunction with the flowchart. In the first example, if the user is working with GUR 4150, or an UHMWPE that satisfies ASTM F648 Type 2 criteria in general, then, based on Figs. 25-27, only the elongation will fall below the ASTM limit (i.e., 300%) over the dose range of interest, i.e., 0 to 25 Mrad, and this occurs at about 6 Mrad. Thus, 35 the maximum allowable dose is 6 Mrad and, from the wear vs dose plot (Fig. 22), it can be seen that a 6 Mrad dose will provide a wear rate of about 7 to 8 mm³ per million cycles. This is about a 78% or more reduction over the 33.1 mm³ per million cycles shown for non-remelted polyethylene gamma irradiated to 3.1 Mrad in air. If this reduction in wear 40 rate is sufficient for the user's purpose, then his goal is achieved. Note however, that the elongation vs dose plot (Fig. 27) shows virtually the same behavior whether the polyethylene is remelted or not, so if the above 78% reduction is not sufficient for the user's purpose, then the user 45 would have no choice but to increase the radiation dose, as annealing is also not likely to affect the elongation to break, for the reasons discussed above.

50 In a second example, a user requires a lower limit on tensile strength at break at 40 MPa, and wishes to produce a material with wear no more than 1 mm³ per million cycles. The wear vs dose curve (Fig. 22) shows that a dose of about 15 Mrad is required to produce a polyethylene with the desired amount of wear resistance. However, the tensile

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strength at fracture vs dose curve shows that the tensile strength at 15 Mrad for a remelted material is about 36 Mpa. 20 Since this is below the user's acceptable limit of 40 Mpa, he can either use a smaller radiation dose and, therefore, accept a smaller improvement in wear rate (i.e., if he wishes to remelt his material) or he can try annealing 25 instead of remelting since, depending on the time/temperature combination used, annealing can be expected to produce a polymer with a value of tensile strength between the limits indicated by the curves for non-remelted and remelted polymer (Figs. 25 and 26). As shown on these 30 figures, the tensile strength at 15 Mrad for a non-remelted material is about 46 Mpa, well above the user's limit of 40. So, with minimal trial and error, the user can identify an 35 annealing time and temperature that, when applied to a polyethylene that has been exposed to 15 Mrad radiation, has a tensile strength of the required 40 Mpa. Again, based on the wear test results, the user knows that he does not have to re-do the wear vs dose curve for all of the various annealing treatments he tries, in order to identify the dose necessary to produce the desired improvement in wear resistance. 40

Having described the invention, the following examples are presented to illustrate and support the invention, and are not to be construed as limiting the scope of the invention.

45

EXAMPLES

The nominal dose of radiation applied to implants at a commercial radiation facility typically varies within a range. 50 Therefore, in the following examples, the average gamma radiation doses are given, such as average gamma radiation doses of 3.3, 26.5, and 28 Mrad. The average of 3.3 Mrad was arrived at by averaging the minimum and maximum

20 doses, e.g., a minimum of 3.28 and a maximum of 3.45 Mrad. Similarly, for example, the average of 26.5 was based on averaging a minimum of 25.14 and a maximum of 27.70 Mrad; and the average of 28 was based on averaging a minimum of 26.01 and a maximum of 30.30 Mrad.

25 EXAMPLE 1: EFFECT OF RADIATION ATMOSPHERE AND DOSE ON THE PHYSICAL PROPERTIES OF UHMWPE

Experimental Details

30 Commercial-grade UHMWPE extruded bars (GUR 4150, Poly Hi Solidur), with a weight average molecular weight of 5-6 x 10⁶, were used as received. The 8mm thick specimens were cut from the bars and irradiated with gamma-rays at room temperature either in ambient air or in a vacuum chamber at 35 SteriGenics International (Tustin, CA) to average doses ranging from 3.3 to 250 Mrad. Radiation was delivered at a dose rate of 0.2 Mrad/hr. For 250 Mrad, the dose rate was 4 Mrad/hr. Cobalt-60 was used as a source of gamma radiation. A subset of the 8mm thick specimens that had been irradiated in vacuum was remelted in a vacuum oven by heating from room 40 temperature to 145°C slowly (at about 0.3°C/min.) and maintaining at 145°C for one hour. After remelting, the specimens were slowly cooled to room temperature.

45 The physical properties of the disk specimens before and after irradiation and remelting were characterized by DSC, gel content analysis and FTIR.

Gel Content Analysis

50 The gel content of each material was analyzed as a function of depth from the surface. 100 µm thick sections (about 50 mg) were microtomed across the specimen. Extraction of the sol-fraction was performed by boiling in p-xylene for 24 hours, with 0.5 wt% of antioxidant (2,6-di-t-butyl-4-methyl phenol) added to prevent oxidation. For

20 highly oxidized sections from the surface layer, which tended to break up during boiling, the specimens were wrapped in PTFE membrane filter (0.5 μm pore size) to avoid loss of gel. After extraction, the specimens were de-swollen in acetone and dried at 60°C in a vacuum oven to constant weight. The gel fraction was determined from the 25 ratio of the weight of the dried-extracted material to that of the dry non-extracted material.

Differential Scanning Calorimetry (DSC)

30 For DSC measurements, samples were cored and microtomed into 200 μm thick sections across the depth. Specimens (~4 mg) were heated from 50°C at 10°C/min in a differential scanning calorimeter (Perkin-Elmer DSC-4) to 170°C. The melting temperature was identified from the peak of the 35 melting endotherm. Indium was used for calibration of the temperature and heat of fusion. The heat of fusion was determined by comparing the area under the melting endotherm to the area of fusion of an indium sample having a known 40 heat of fusion of 28.4 J/g, and divided by 292 J/g, the heat of fusion of an ideal polyethylene crystal, to get the degree of crystallinity.

Results and Discussion

45 As shown in Fig. 1, irradiation increased the crystallinity of the 8mm thick specimens of UHMWPE from about 55% to 60-66%, with considerable overlapping for the different doses. Similar changes were observed with the samples that were irradiated in air. The gel content (i.e., the extent of crosslinking) (Fig. 2) also increased with 50 increasing radiation dosage. Importantly, crosslinking increased markedly moving from the surface into the middle of each specimen, reaching about 92% for the 3.3 Mrad dose. Apparently, the oxygen present in the vacuum chamber was sufficient to cause the increased oxidation and decreased

20 crosslinking of the surface layer. Thus, our method, i.e., of irradiating a bar and machining away the surface is more effective and efficient than use of a vacuum or other low oxygen atmosphere in producing a final product with minimal oxidation of the bearing surface. For reference (Fig. 3), chemically crosslinked polyethylene (PE) (1% peroxide, irradiated in air) (Shen, F.W. et al. J. of Poly. Sci. Part B: Poly Phys 34:1063-1077 (1996)), which exhibits very low wear, has a gel content of about 90% at about 100 microns from the surface, rising to a maximum of nearly 100% in the center.

30 In a second phase of this example, the 8mm thick disks that had been irradiated in vacuum were remelted by heating to 145°C for one hour, and slowly cooled. This reduced the peak melting temperature, the degree of crystallinity and the crystal size. For example (Fig. 4), the crystallinity of the 3.3 Mrad specimens was reduced from the range of 60-35 65% to the range of 50-53% by remelting.

40 In addition, during remelting, residual free radicals that were formed by the irradiation apparently recombined and increased the total crosslinking (as evident from the increased gel content, Fig. 5). Extinguishing free radicals in this manner, in turn, further reduces the oxidation that would otherwise occur when the cups are stored on the shelf or exposed to body fluids after implantation.

45 The lower gel content (crosslinking) near the surface (Fig. 3) was due to oxidation of the surface layer at the time of irradiation. Thus, it can be expected that the polymer of the surface layer would have less wear resistance than that in the center of the specimen. In the method presented in this application, this gradient would not be 50 present, since the surface layer would be removed during machining of the final implant from the irradiated bar or block.

20 The crystallinity and gel content of the irradiated 8mm thick disks, with and without remelting, are compared in Figs. 4 and 5, respectively.

EXAMPLE 2: WEAR TESTING OF RADIATION CROSSLINKED CUPS WITH AND WITHOUT REMELTING

25

Experimental Details

30 Six extruded bars of UHMWPE (GUR 4150), each 3 inches in diameter, were exposed to 3.3 or 28 Mrad of gamma radiation at a dose rate of 0.2 Mrad per hour in ambient air (SteriGenics, Inc., Tustin, CA). Two bars for each radiation dose were then remelted by heating in an oven in ambient atmosphere from room temperature to 150°C at about 0.3°C per minute and holding at 150°C for five hours, and then slow-cooling to room temperature. The crystallinity and gel content of these four materials were measured across the cross section of extra samples of each bar using differential scanning calorimetry (DSC) and gel content analysis.

35 The results are summarized in Tables 1 and 2.

40 Four sets of acetabular cups were machined from bars of each of the four materials at a commercial machining shop (Bradford and Meneghini Manufacturing Co., Santa Fe Springs, CA). Each cup had a 2 inch outer diameter (O.D.) and 1.26 inch inner diameter (I.D.), and 1 inch outer radius and 0.633 inch inner radius (Fig. 6). Wear tests were run on 45 two sets of three cups for each radiation dose that had been remelted, and two sets of three cups for each dose that had not been remelted. The bars were intentionally used with larger diameters than the final cups so that the process of machining away the outer 0.5 inches of each bar removed the most oxidized, most crystalline, least crosslinked surface layer which is about 0.5 to 1.0 mm thick. In this manner, 50 the bearing surface of each cup consisted of material from near the center of the bar, i.e., the most crosslinked,

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least crystalline, least oxidized region, which is predicted
20 to be the most wear resistant.

Since acetabular cups used in patients must first be
sterilized by some acceptable means, the test cups in this
study were sterilized prior to wear testing using ethylene
oxide at the appropriate dose for clinical implants. Ethyl-
ene oxide was chosen instead of additional gamma irradiation
25 (e.g., 2.5-4.0 Mrad) in order to confine the results to the
effects of the original 3.3 or 28 Mrad doses used to
crosslink the materials.

Prior to wear testing, the cups were pre-soaked in
30 distilled water for three weeks to minimize additional fluid
absorption during the wear test, thereby making the weight
loss method for wear measurement more accurate. For the
wear test, the cups were enclosed in polyurethane molds and
pressed into stainless steel holders (Fig. 7). Each holder
35 was fitted with an acrylic chamber wall to contain the
lubricant. The chambers were mounted on the hip simulator
wear machine, with each cup bearing against a ball of
cobalt-chromium alloy (conventional hip replacement femoral
balls were used, with implant-quality surface finish). The
40 ball-cup pairs were subjected to a physiological cyclic load
with a peak load of about 2000 Newtons (Paul, JP., "Forces
transmitted by joints in the human body". In Lubrication
45 and Wear in Living and Artificial Human Joints. Proc Instn
Mech Engrs 1967;181 Part 3J:8-15) and the cups were oscil-
lated against the balls through a bi-axial 46° arc at 68
cycles per minute. Each test station on the simulator (Fig.
50 7) contains a self-centering unit 5, the acetabular cup 6, a
dual axis offset drive block 7, a test chamber 8, serum
lubricant 9 and a femoral ball 10. The arrow indicates the
direction of the computer controlled simulated physiological
load applied to the simulated hip joint.

During the test, the bearing surfaces were kept im-
mersed in bovine blood serum to simulate lubrication in the

20 human body. Sodium azide at 0.2% was added to the serum to retard bacterial degradation, and 20 mM ethylene-
25 diaminetetraacetic acid (EDTA) was added to prevent precipitation of calcium phosphate onto the surface of the balls (McKellop, H. and Lu, B., "Friction and Wear of Polyethylene-metal and Polyethylene-ceramic Hip Prostheses on a Joint Simulator, Transactions of the Fourth World Biomaterials Congress, Berlin, Apr. 1992, p. 118). A poly-
30 ethylene skirt covered each test chamber to minimize airborne contaminants.

35 At intervals of 250,000 cycles, the cups were removed from the machine, rinsed, inspected under light microscopy and replaced in fresh lubricant. At intervals of 500,000 cycles, the cups were removed, cleaned, dried and weighed to indicate the amount of wear. After inspection under light microscopy, the cups were replaced on the wear machine with fresh lubricant and testing was continued to a total of three million cycles. One million cycles is approximately the equivalent of one year's walking activity of a typical patient.

40 The weight loss was corrected for the effects of fluid absorption (which masks wear) by increasing the apparent weight loss of the wear test cups by the mean weight gain of three control cups of each material that were also immersed in serum and cyclically loaded on a separate frame, but without oscillation. The corrected rate of weight loss was 45 converted to volume loss by dividing by the approximate density of UHMWPE (0.94 gm/cc). The mean weight loss (after soak correction) and the standard deviation was calculated for each of the four types of materials at each weighing interval. The wear rate of each cup was calculated by applying linear regression to the wear data for the entire 50 three million cycles. The mean wear rates and standard deviations also were calculated for each type of material.

Results

20 Fig. 8 shows the soak-corrected wear (volume loss) of three cups of each material as a function of wear cycles. Fig. 9 shows the average wear (volume loss) of three cups of each material as a function of wear cycles. The individual wear rates and the mean values for each type of material are listed in Table 3. The most wear occurred with the cups subjected to 3.3 Mrad without remelting. These averaged 21.1 mm³ per million cycles.

25 30 35 The wear of the cups subjected to 3.3 Mrad with remelting averaged 18.6 mm³ per million cycles, or 12% lower wear than for the non-remelted 3.3 Mrad cups. The cups subjected to 28 Mrad had much lower wear rates than the 3.3 Mrad cups, and the rates were similar, whether or not the material had been remelted. That is, the average wear rate of the non-remelted 28 Mrad cups was about 1.2% that of the non-remelted 3.3 Mrad controls, and the average wear rate of the remelted 28 Mrad cups was about 1.7% of the same controls.

Discussion

40 45 50 The results of the wear test clearly demonstrated the improved wear resistance of the UHMWPE acetabular cups that resulted from exposure to 28 Mrad gamma radiation. Apparently, the crosslinking generated by the higher radiation dose reduced the wear rates to less than a few percent of the control value (3.3 Mrad). The minimum amount of wear debris necessary to induce clinically significant osteolysis and other problems in a specific patient has not been established, and it may vary among patients. Nevertheless, a material which reduces the wear rate to the very low levels exhibited by the 28 Mrad cups in this study would be very likely to provide a large margin of safety over currently used materials.

The wear curves for both of the 28 Mrad specimens (Figs. 8 & 9) were slightly negative on the first weighing

20 at 0.5 million cycles. This was most likely due to a slight under-correction for fluid absorption (that is, the wear test cups absorbed slightly more water than the soak controls, and the error between the two was greater than the weight loss due to wear, producing a negative wear value).
25 If this assumption is correct, then the overall wear rates for the two 28 Mrad sets were somewhat smaller, and possibly closer together, than the values indicated in Table 3.

EXAMPLE 3: ARTIFICIAL AGING OF RADIATION-CROSSLINKED UHMWPE

30 MATERIALS

35 Six UHMWPE (GUR 4150) extruded bars (3" diameter) were gamma irradiated in air, three bars each at 3.3 or 28 Mrad, at a dose rate of 0.2 Mrad/hour. For each radiation dose, two bars were then remelted by heating in an oven at ambient atmosphere from room temperature to 150°C at about 0.3°C/min, holding at 150°C for 5 hours and slowly cooling to room temperature, and the third bar was not remelted. A 40 13 mm (0.5 inch) layer of the outer diameter of the treated (remelted) and untreated (non-remelted) bars was machined away to remove the most oxidized, least crosslinked surface layer. The bars were used to produce specimens for the artificial aging tests described here and for the wear tests described in EXAMPLE 2.

45 To examine the effect of artificial aging on these four materials (3.3 and 28 Mrad, remelted and not remelted), 8 mm thick disks were cut from these 2 inch diameter cores and were heated in an oven slowly (~ 0.2 °C/min) to 80 °C at ambient atmosphere and held at 80°C for 10, 20 or 30 days. 50 In addition, one acetabular cup for each of the four conditions (3.3 and 28 Mrad, remelted and not remelted) that had been fabricated at the same time as the wear test cups of

EXAMPLE 2 and stored in air for about 5 months was cut into
20 four pieces and aged at 80°C for the same periods.

The gel content analysis and DSC method are as de-
scribed in EXAMPLE 1, above.

Fourier Transform Infrared Spectroscopy (FTIR)

25 FTIR measurements were performed on the above speci-
mens. Segments about 5 mm wide were cut from each polyeth-
ylene specimen and the segments were microtomed into 200 μm
thick slices. The oxidation profiles, as indicated by the
carbonyl concentration, were measured using a Mattson Po-
30 laris FTIR (model IR 10410) with a Spectra-Tech IR plan
microscope. Spectra were collected in 100 μm steps from the
surface to the middle of the specimen, using 64 scans summa-
tion at a resolution 16 cm^{-1} with a MCT (Mercury Cadmium
Telluride) detector. The carbonyl group concentration was
35 indicated by the ratio of the peak height of the ketone
absorption band at 1717 cm^{-1} to the height of the reference
band at 2022 cm^{-1} (- CH_2 - vibration).

RESULTS

40 The oxidation profiles as a function of depth are shown
in Figs. 10-13. As shown in Fig. 10 for the 3.3 Mrad, non-
remelted material, oxidation increased with increasing aging
time. In contrast, the 3.3 Mrad, remelted material (Fig.
45 11) showed almost no oxidation for 10 and 20 days aging, but
some oxidation for 30 days aging. However, the oxidation
peak at the surface with remelting was about 50% of that at
the surface without remelting (Fig. 10). For the 28 Mrad,
non-remelted UHMWPE (Fig. 12), the oxidation showed a
greater increase with increasing aging time than the 3.3
50 Mrad, un-remelted material. Again, oxidation was much lower
with remelting, i.e., the 28 Mrad, remelted UHMWPE (Fig. 13)
essentially exhibited no oxidation after 20 days aging (Fig.

13), and the oxidation peak at the surface after 30 days was
20 only about 1/3 that without remelting (Fig. 12).

Similarly, with the acetabular cups stored in air for 5
months and then aged for 20 days at 80°C, the remelted
materials (3.3 or 28 Mrad) showed no oxidation (Fig. 14),
25 while the non-remelted cups (3.3 or 28 Mrad) showed substantial
oxidation (Fig. 14), especially for 28 Mrad UHMWPE, and
with a subsurface oxidation peak in both non-remelted materials.

Since crosslinking of UHMWPE reduces its solubility,
the percent of undissolved material (gel content) is an
30 indirect indication of the amount of crosslinking. The gel
content as a function of depth for various conditions are
shown in Figs. 15 to 18. As shown in Fig. 15 for 3.3 Mrad,
non-remelted material, the gel content (i.e., crosslinking)
decreased with increasing aging time. There was a strong
35 gradient of gel content in the highly oxidized surface
regions after 30 days aging, i.e., increasing from a minimum
on the surface to a maximum about 2 mm below the surface.
Near the surface, the gel content was highest (91%) in the
un-aged specimen, and decreased with increasing aging time
40 to less than about 5% in the same region for the 30 day aged
specimen. In contrast, the remelted materials (Fig. 16)
showed much less reduction in gel content in the surface
regions than the non-remelted materials. That is, comparison
45 of Fig. 17 (28 Mrad, non-remelted) and Fig. 18 (28 Mrad,
remelted) showed that the remelted UHMWPE had much higher
retention of gel content (i.e., crosslinking).

The results of the DSC measurements indicated the
degree of crystallinity as a function of depth for various
50 materials aged for 30 days at 80°C, as shown in Fig. 19.
Near the surface, the degree of crystallinity was 83% for
the 28 Mrad, non-remelted material after aging, compared to
65% before aging. The high level of crystallinity and
increased brittleness of the surface zone of the aged mate-

rial often resulted in fragmentation of a layer about 1 mm
20 thick during microtoming. In contrast, the 28 Mrad remelted
material showed less increase in crystallinity in the sur-
face regions due to aging, and no brittle zone was observed.
Similarly, due to aging, the 3.3 Mrad non-remelted material
exhibited an increase in crystallinity from 60% to about
25 78%, and the surface layer was again brittle, although not
as brittle as with the 28 Mrad, non-remelted material.

DISCUSSION

Irradiation of UHMWPE produces crosslinking, chain
30 scission and the formation of free radicals. If oxygen is
present, it may react with the free radicals to form oxi-
dized species, leading to additional chain scission (reduc-
tion in molecular weight) and an increase in crystallinity.
Since polymer crystallites melt and become amorphous above
35 the melting temperature, molecular chain movements and
rotations are increased, favoring the recombination of free
radicals. The results of the present experiments showed
that remelting at 150°C apparently caused the residual free
radicals to decay and/or to recombine to form crosslinks,
40 leading to an increased gel content. Therefore, remelting
is an effective way to extinguish free radicals, making the
material less susceptible to long-term oxidation and poten-
tially improving the long-term wear resistance, as evident
45 from the results of the artificial aging experiments, where
there was much less oxidation of the remelted materials.

For a crosslinked polymer, oxidative degradation
cleaves the molecules and leads to a reduction in gel con-
tent. This was evident in the present experiments from the
reduced gel content after aging, particularly with the non-
50 remelted materials (Figs. 15 to 18). That is, the distribu-
tion of oxidation, as indicated by the profiles measured by
FTIR, was inverse to the gel content within the material;
the higher the oxidation, the lower the gel content

20 (crosslinking). Since remelting extinguishes free radicals and increases gel content, thereby reducing the susceptibility to oxidation, the remelted materials (3.3 and 28 Mrad) had a much greater gel content after artificial aging than the non-remelted materials.

25 An appropriate amount of crosslinking of UHMWPE can improve its wear resistance. The high level of crosslinking in the UHMWPE caused by the 28 Mrad gamma irradiation, as evident from the high gel content (EXAMPLE 2), apparently contributed to the much greater wear resistance exhibited by the acetabular cups tested in EXAMPLE 2. In addition, as 30 shown in EXAMPLE 3, remelting of the irradiated UHMWPE markedly reduced the residual free radicals, rendering the material much more resistant to subsequent oxidation and, therefore, resistant to a reduction in crosslinking, which can be of substantial benefit for implants in long-term 35 clinical use.

EXAMPLE 4: WEAR TESTING OF IRRADIATED CUPS WITH AND WITHOUT ARTIFICIAL AGING

40 Materials and Methods

The wear testing of irradiated cups with and without remelting was described in EXAMPLE 2. Effects of artificial aging on the physical properties of irradiated UHMWPE, with and without remelting, were described in EXAMPLE 3. To 45 examine the resistance of crosslinked cups to thermal-induced oxidation, and the effect of such oxidation on the wear of irradiated cups with and without remelting, two acetabular cups for each of the four conditions (3.3 and 28 Mrad, remelted and not remelted) that had been wear tested 50 for 3 million cycles as described in EXAMPLE 2, were heated in an oven slowly (~ 0.2 °C/min) to 80 °C at ambient atmosphere and held at 80 °C for 20 days, with one acetabular cup for each of the four conditions being stored in ambient

20

air. The oxidation profile after 20-day aging for each condition was shown in Fig. 14, EXAMPLE 3.

25

Prior to wear testing, the cups were pre-soaked in distilled water for four weeks to minimize additional fluid absorption during the wear test, thereby making the weight loss method for wear measurement more accurate. The details for the wear test were described in EXAMPLE 2.

Results

30

Fig. 20 shows the combined soak-corrected wear (volume loss) for the cups before aging (3.3 and 28 Mrad, remelted and not remelted) during the first 3 million cycles (same data as EXAMPLE 2) and for the same cups, after two cups of each material had been artificially aged, from 3 to 7 million cycles. The individual wear rates and the mean values for each type of material, calculated by linear regression, are listed in Table 4.

35

All cups subjected to 3.3 Mrad with remelting showed comparable wear rates, whether or not the material had been remelted or remelted and aged. Wear was negligible for all of the cups subjected to 28 Mrad, whether or not these were remelted, and whether or not they were aged.

Discussion

45

The results of the wear test clearly demonstrated the improved wear resistance of the UHMWPE acetabular cups that resulted from exposure to 28 Mrad gamma radiation. Apparently, the minor oxidation at the surface (Fig. 14) of the highly crosslinked acetabular cups (28 Mrad, without remelting) induced by the artificial aging, had very limited effect on the wear resistance. Although a substantial oxidation peak occurred about 0.4 mm below the surface, because of the very high wear resistance of the 28 Mrad cups, the total penetration due to wear was too shallow to reach this sub-surface oxidized zone, even after 4 million cycles.

For the non-remelted 3.3 Mrad cups, subsurface oxidation, peaking at about 1 mm below the surface (Fig. 14), occurred after aging in air at 80 °C for 20 days. Since the total depth of penetration of these cups was about 300 microns (at 7 million cycles), the full effect of this subsurface oxidation would not become apparent until a much larger number of wear cycles.

Nevertheless, the sub-surface oxidation in the non-remelted cups (EXAMPLE 3, particularly for the 28 Mrad specimen) leads to reduced molecular weight, a reduction in crosslinking (as indicated by gel content) and an increased crystallinity and brittleness, all of which can contribute to reductions in mechanical properties such as fatigue strength and, eventually, a reduction in wear resistance. Although remelting had no apparent effect on the wear resistance of the aged cups in the present example, the elimination of free radicals by remelting improves the long-term resistance to oxidation, thereby improving the long-term wear resistance *in vivo*.

EXAMPLE 5: WEAR TESTING OF GAMMA-IRRADIATED UHMWPE WITH
MULTIPLE DOSES

Materials and Methods

In EXAMPLE 2, we demonstrated the improved wear resistance of UHMWPE acetabular cups that resulted from exposure to 28 Mrad gamma radiation, as compared to cups irradiated to 3.3 Mrad. The average wear rate of the 28 Mrad cups was less than 2% of that of the 3.3 Mrad cups (i.e., a dose within the normal 2.5 to 4.0 Mrad range used to sterilize implants). To examine the wear as a function of radiation dose and, thereby, determine an optimum dose for reducing wear, extruded bars of GUR 4150 UHMWPE, 3" diameter x 15" long, were gamma irradiated in air, three bars at each dose of 4.5, 9.5, 14.5, 20.2 or 24 Mrad (SteriGenics, Inc.,

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20 Corona, CA), at a dose rate of 0.45 Mrad/hour. Additional bars were irradiated in air to 50 or 100 Mrad (SteriGenics Inc., Tustin, CA), at a dose rate of 0.67 Mrad/hour. For each radiation dose, two bars were then remelted by heating in an oven in ambient atmosphere from room temperature to 150 °C at about 0.3 °C/min, holding at 150 °C for 5 hours and then slowly-cooled to room temperature, with the third bar not being remelted. The irradiated-remelted bars were used to produce acetabular cups for the wear tests.

30 Seven sets of acetabular cups were machined from the irradiated-remelted bars for each of the seven doses at a commercial machining shop (Bradford and Meneghini Manufacturing Co., Santa Fe Springs, CA). Each cup had a 2" O.D. and 1.26" I.D., with 1" outer radius and 0.63" inner radius (Fig. 6). Wear tests were run on the remelted specimens, using two cups for each radiation dose from 4.5 to 24 Mrad, and one cup each for 50 and 100 Mrad. The bars were intentionally used with larger diameters than the final cups so that the process of machining away the outer layer of each bar, about 0.5 inch thick, effectively removed the most oxidized, most crystalline, least crosslinked surface layer (about 0.5 to 1.0 mm). In this manner the bearing surface of each cup consisted of material from near the center of the bar, i.e., the most crosslinked, least crystalline, least oxidized region, which was expected to be the most wear resistant.

45 Because acetabular cups used in patients must first be sterilized by some acceptable means, the test cups in this study were sterilized prior to wear testing using ethylene oxide at the appropriate dose for clinical implants. Ethylene oxide was chosen instead of additional gamma irradiation (e.g., 2.5-4.0 Mrad) in order to focus the results on the effects of the radiation doses used to crosslink the materials. Prior to wear testing, the cups were pre-soaked in distilled water for four weeks to minimize additional fluid

20 absorption during the wear test, thereby making the weight loss method for wear measurement more accurate. The details for the wear test method were described in EXAMPLE 2.

Results

25 Fig. 21 shows the soak-corrected wear (volume loss) of each material (three cups for 3.3 Mrad from EXAMPLE 2, two cups each for radiation dose from 4.5 to 24.5 Mrad, and one cup each for 50 and 100 Mrad). The individual wear rates, determined by linear regression, and the mean values for each type of material are listed in Table 5. At about 2.1 million cycles, there was a temporary overloading of the test cups, due to a malfunction of the computer controller. Although this overload had only a minor effect on the wear rates of the cups, the cup irradiated to 100 Mrad cracked and was, therefore, removed from the test.

30 35 Fig. 22 shows the average wear rate (volume loss from 1 to 5 million) of each type of material, that had been re-melted (denoted in the figure by darkened circles) and that had not been re-melted (denoted in the figure by an open circle), as a function of dose.

40 The wear of the cups subjected to 3.3 or 4.5 Mrad with remelting averaged 17.5 or 9.3 mm³ per million cycles, respectively, showing about 13% or 54% lower wear than for the 3.3 Mrad non-re-melted cups (20.1 mm³ per million cycles). In contrast, the wear rate of the 9.5 Mrad remelted 45 cups averaged 2.2 mm³ per million cycles, i.e., about 89% lower than for the 3.3 Mrad non-re-melted cups. For radiation doses greater than 9.5 Mrad, minimal systematic wear occurred, such that, compared to that with 3.3 Mrad non-re-melted cups, the wear rates were about 94% lower for the 50 14.5 Mrad remelted cups, and minimal wear (>99% reduction) for the 20.2 Mrad remelted cups.

"Negative" wear rates were calculated for the cups given 24 Mrad or greater doses. Apparently, these cups

20 absorbed more water than the soak control cups, and the error between the two was greater than the weight loss due to wear, giving a net gain in weight.

Discussion

25 The results clearly demonstrated that the wear resistance of UHMWPE acetabular cups were improved substantially with increasing radiation dose over the range of 4.5 to 9.5 Mrad (i.e., with increasing crosslinking), such that wear was too small to accurately quantify for doses exceeding about 20 Mrad. Since, in addition to improving wear resistance, 30 radiation induced crosslinking may degrade other physical properties, such as elongation to failure and fatigue strength, the dose-response curve developed in the present example provides the opportunity to select an optimum dose, i.e., one that provides the desired amount of improvement in wear resistance with a minimum reduction in other physical properties. The procedure for arriving at the choice of dose for a particular *in vivo* application is 35 described in this application.

40 UHMWPE acetabular cups that had been compression molded and then exposed to 3.1 Mrad gamma radiation in air but were not thermally treated (i.e., typical of commercially used implants over the past two decades), showed an approximate wear rate of 33.1 mm³/million cycle using the procedure of the wear test described in EXAMPLE 2, above. When compared 45 to these conventional UHMWPE acetabular cups, the acetabular cups of the present invention (i.e., irradiated bar stock, remelted and machined into cups) show the following percentage reduction in wear rate: for the 3.3 Mrad remelted acetabular cup from EXAMPLE 2, above (about 47% reduction in wear rate); 4.5 Mrad remelted acetabular cup from EXAMPLE 5, above (about 72% reduction in wear rate); 9.5 Mrad remelted acetabular cup from EXAMPLE 5, above (about 93% reduction in wear rate).

EXAMPLE 6: PHYSICAL CHARACTERIZATION OF GAMMA-IRRADIATED
20 UHMWPE WITH OR WITHOUT REMELTING

Materials and Methods

The materials for physical characterization were the same as the wear tested materials described in EXAMPLE 5. The materials included UHMWPE extruded bars (3" in diameter) gamma irradiated to 3.3, 4.5, 9.5, 14.5, 20.2, 24, 50 and 100 Mrad, with or without remelting, and the non-irradiated bars. 8 mm thick disks were cut out of irradiated bars with or without remelting, and sterilized with ethylene oxide. The specimens for DSC and swelling measurements were cut out of the center of the 8 mm thick disks. The DSC measurement for crystallinity and melting temperature with sample weighing about 4 mg was described in EXAMPLE 1. For swelling measurements, 1 mm thick sheet weighing about 0.5 gram was cut out of the center of the 8 mm thick disk, and extraction of the sol-fraction was performed in boiling p-xylene for 72 hours, with 0.5 wt % antioxidant (2,6-di-t-butyl-4-methyl phenol) being added to prevent oxidation. After extraction, the gel was transferred to fresh p-xylene and allowed to equilibrate at 120°C for 2 hours. The swollen gel was then quickly transferred to a weighing bottle, covered and weighed. The data was obtained as the average of five measurements. After measurements, samples were deswollen in acetone and then dried at 60°C in a vacuum oven to a constant weight. The gel fraction was determined as the ratio of the weight of the dried extracted to the initial dry non-extracted network. The degree of swelling was calculated as the ratio of the weight of the swollen gel to the dried extracted gel. The degree of swelling was used to calculate the network chain density, number-average molecular weight between crosslinks and crosslink density, according to the theory of Flory and Rehner (Shen et al., J. Polym. Sci., Polym. Phys., 34:1063-1077 (1996)). For examining the

20 oxidation profiles of the extruded bars irradiated and remelted in air, a two hundred micron thick section was microtomed perpendicular to the bar surface and examined by FTIR as a function of depth from the bar surface.

Results and Discussion

25 The melting temperature and crystallinity for non-irradiated, and irradiated (with and without remelting) materials are shown in Table 6. The degree of swelling, average molecular weight between crosslinks, crosslink density and gel content are shown in Table 7. After irradiation, the melting temperature and crystallinity increased, ranging from 135.3 to 140.2°C, and about 60 to 71%, respectively, over the dose range studied. Remelting of the irradiated bars resulted in reductions in the melting temperature and crystallinity, ranging from about 131 to 135°C, and about 51 to 53%, respectively.

30 As shown in Table 7, with increasing radiation dose, the degree of swelling and average molecular weight between crosslinks decreased, while the crosslink density increased. The gel content, in general, increased with radiation dose, but reached a plateau region at about 9.5 Mrad. With remelting, the degree of swelling and average molecular weight between crosslinks for bars irradiated up to 9.5 Mrad were significantly reduced, but remained almost unchanged after 9.5 Mrad. The crosslink density increased, after remelting, with dose up to 9.5 Mrad and then remained almost unchanged. The gel content, generally, increased after remelting.

40 45 The oxidation profiles for the 9.5 and 24 Mrad materials, after remelting at 150°C in air for 5 hours, as a function of depth from the bar surface are shown in Fig. 24. The results clearly showed that the oxidation drops tremendously within 1 mm, and the most oxidized layer is about 1 mm deep below the surface, after irradiation and remelting in air.

20

EXAMPLE 7: TENSILE PROPERTIES OF GAMMA-IRRADIATED UHMWPE AT
VARIOUS DOSES, WITH OR WITHOUT REMELTING

25

Materials and Methods

The materials for tensile test are the same as the wear tested materials described in EXAMPLE 5, above. The materials included UHMWPE extruded bars (3" in diameter) gamma irradiated to 4.5, 9.5, 14.5, 20.2, and 24 Mrad, with or without remelting, and non-irradiated bars. Five tensile specimens each was machined out of the center of the 3" diameter bars according to ASTM F648-96 and D-638 (type IV). Tensile tests were performed using an servo-hydraulic tensile test machine at speed of 2 inches/min.

30

Results and Discussion

35

The tensile strength at yield, elongation, and tensile strength (ultimate) at breaks are shown in Table 8. The average tensile properties as a function of radiation dose are shown in Figs. 25-27. The tensile strength at yield after irradiation was higher than that of non-irradiated material, and slightly increased with radiation dose.

40

Remelting of the irradiated bars resulted in a reduction in tensile strength at yield, and the strength remained almost constant over the dose range studied (Fig. 25). The tensile strength (ultimate) and elongation at break decreased with increasing doses (Figs. 26-27). Remelting resulted in further reduction in ultimate tensile strength over the dose range. However, remelting had almost no effect on the elongation at break over the same dose range.

45

50

All publications and patent applications mentioned in this Specification are herein incorporated by reference to the same extent as if each of them had been individually indicated to be incorporated by reference.

20 Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be obvious that various modifications and changes which are within the skill of those skilled in the art are considered to fall within the scope of the appended claims. Future technological advancements which allows for obvious changes in the basic invention herein are also within the claims.

25

Table 1 3.3 Mrad

Distance from surface (mm)	Before remelting			After remelting		
	peak melting temperature (°C)	degree of crystallinity (%)	gel content (%)	peak melting temperature (°C)	degree of crystallinity (%)	gel content (%)
34.8 - 35	135.3	59.6	91	131.4	52.5	94.7
35.8 - 36	135.4	60.2	91	131.5	51.2	94.7
36.8 - 37	135.3	60.5	91	131.4	51.9	94.7
37.8 - 38 (center)	135.3	60	91.1	131.3	52	95

Table 2 28 Mrad

Distance from surface (mm)	Before remelting			After remelting		
	peak melting temperature (°C)	degree of crystallinity (%)	gel content (%)	peak melting temperature (°C)	degree of crystallinity (%)	gel content (%)
34.8 - 35	139.8	65.1	95.8	135	52	97.7
35.8 - 36	139.8	64.2	95.8	134.8	52.1	97.7
36.8 - 37	139.7	64.5	95.8	134.9	52.5	97.7
37.8 - 38 (center)	139.7	65.3	95.8	134.9	52.7	97.7

Table 3

Cup #	Material	Wear Rate (mm ³ /million cycles)	Mean Wear Rate ± Std Deviation
N11	3.3 Mrad Not remelted	20.8	21.1 ± 0.3
N16		21.2	
N17		21.4	
R21	3.3 Mrad Remelted	17.7	18.6 ± 1.3
R26		20.1	
R27		18.0	
N35	28 Mrad Not remelted	0.29	0.25 ± 0.03
N31		0.24	
N32		0.24	
R48	28 Mrad Remelted	0.36	0.36 ± 0.001
R45		0.35	
R49		0.36	

Table 4

Cup #	Material	0 - 3 Million Cycles (non- aged)		3 - 7 Million Cycles		
		Wear Rate (mm ³ /million cycles)	Mean Wear Rate ± Std Deviation	Conditions	Wear Rate (mm ³ /million cycles)	Mean Wear Rate ± Std Deviation
N11	3.3 Mrad Not remelted	20.8	21.1 ± 0.3	non-aged	21.2	-
N16		21.2		aged	21.5	21.8 ± 0.5
N17		21.4		aged	22.2	
R21	3.3 Mrad Remelted	17.7	18.6 ± 1.3	non-aged	17.5	-
R26		20.1		aged	19.2	19.8 ± 1.0
R27		18.0		aged	20.5	
N35	28 Mrad Not remelted	0.29	0.25 ± 0.03	non-aged	0.03	-
N31		0.24		aged	- 0.47	- 0.71 ± 0.3
N32		0.24		aged	- 0.93	
R48	28 Mrad Remelted	0.36	0.36 ± 0.001	non-aged	0.47	-
R45		0.35		aged	0.08	- 0.06 ± 0.2
R49		0.36		aged	- 0.20	

Table 5 (1 - 5 million cycles)

Cup #	Material	Wear Rate (mm ³ /million cycles)	Mean Wear Rate ± SD (mm ³ /million cycles)
N11	3.3 Mrad Not remelted	20.46	20.12 ± 0.7 *
N16		19.32	
N17		20.59	
R21	3.3 Mrad Remelted	17.04	17.51 ± 0.48 *
R26		18.0	
R27		17.49	
RA2	4.5 Mrad Remelted	9.93	9.28 ± 0.92
RA3		8.63	
RB3	9.5 Mrad Remelted	2.39	2.22 ± 0.24
RB6		2.05	
RC5	14.5 Mrad Remelted	1.26	1.17 ± 0.13
RC6		1.08	
RD1	20.2 Mrad Remelted	0.26	0.12 ± 0.2
RD6		-0.02	
RE3	24 Mrad Remelted	-0.49	-0.59 ± 0.13
RE4		-0.68	
RF2	50 Mrad Remelted	-0.8	-
RG1	100 Mrad Remelted	-6.88**	-

*The wear data of the 3.3 Mrad materials in Example 2.

**The wear rate in the period of 1 - 2 million cycles.

Table 6

Samples	Non-remelted		Remelted		Crystallinity (%)
	Melting point (°C)	Crystallinity (%)	Melting point (°C)	Crystallinity (%)	
Non-irrad.	133.8	55	-	-	-
3.3 Mrad	135.3 ± 0.1	60.1 ± 0.4	131.4 ± 0.1	51.8 ± 0.6	
4.5 Mrad	136.2 ± 0.2	65.8 ± 1.6	131.6 ± 0.2	52.0 ± 1.3	
9.5 Mrad	137.1 ± 0	67.1 ± 2.2	134.8 ± 0.2	53.3 ± 2.1	
14.5 Mrad	137.5 ± 0.2	69.6 ± 1.6	135.0 ± 0.1	53.0 ± 1.5	
20.2 Mrad	137.4 ± 0.1	70.8 ± 2.8	135.3 ± 0.1	52.1 ± 1.8	
24 Mrad	137.9 ± 0.3	68.0 ± 1.3	135.2 ± 0.1	51.7 ± 1.2	
50 Mrad	138.9 ± 0.2	67.0 ± 1.3	135.2 ± 0	52.8 ± 0.2	
100 Mrad	140.2 ± 0.3	66.3 ± 2.7	130.8 ± 0.2	52.3 ± 1.7	

Table 7

Samples	Non-remelted			Remelted				
	Degree of swelling	M.W. between crosslinks (g/mol)	Crosslink density (mol%)	Gel content (%)	Degree of swelling	M.W. between crosslinks (g/mol)	Crosslink density (mol%)	Gel content (%)
3.3 Mrad	5.29	8400	0.17	94.7	3.21	2500	0.56	98.1
4.5 Mrad	3.57	3500	0.40	97.8	3.15	2400	0.58	98.4
9.5 Mrad	2.82	1900	0.74	98.6	2.54	1400	1.0	98.9
14.5 Mrad	2.35	1100	1.27	98.7	2.36	1100	1.27	99.2
20.2 Mrad	2.27	1000	1.40	98.8	2.25	1000	1.40	99.2
24 Mrad	2.17	900	1.56	98.7	2.24	1000	1.40	99.1
50 Mrad	1.92	600	2.33	98.7	2.17	900	1.56	99.1
100 Mrad	1.71	400	3.50	98.6	1.71	400	3.50	98.5

Table 8

Materials	Tensile Strength at Yield (MPa)	Tensile Strength at Break (MPa)	Elongation at Break (%)
Non-irradiated	23.3 \pm 0.11	52.1 \pm 4.78	356 \pm 23
Without remelting			
4.5 Mrad	24.9 \pm 0.33	46.9 \pm 2.91	314 \pm 12
9.5 Mrad	25.3 \pm 0.12	47.6 \pm 2.76	251 \pm 8
14.5 Mrad	25.7 \pm 0.25	46.4 \pm 1.20	213 \pm 5
20.2 Mrad	26.2 \pm 0.27	40.2 \pm 2.72	175 \pm 7
24 Mrad	26.4 \pm 0.23	40.0 \pm 5.42	164 \pm 17
After remelting			
4.5 Mrad	21.5 \pm 0.33	45.6 \pm 8.89	309 \pm 20
9.5 Mrad	21.3 \pm 0.60	43.2 \pm 2.80	252 \pm 8
14.5 Mrad	21.8 \pm 0.29	36.8 \pm 1.72	206 \pm 9
20.2 Mrad	21.9 \pm 0.18	34.3 \pm 3.61	185 \pm 8
24 Mrad	21.7 \pm 0.25	32.3 \pm 2.81	160 \pm 19

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We claim:

20

1. A preformed polymeric composition comprising a crosslinked thermally treated polymer.

25

2. The composition of claim 1, wherein the composition possesses one or more of the following characteristics: degree of swelling of between about 1.7 to about 5.3; molecular weight between crosslinks of between about 400 to about 8400 g/mol; and a gel content of between about 95 to about 99 %.

30

3. The composition of claim 1, wherein the preformed polymeric composition is crosslinked by gamma radiation at a dose from about 1 to about 100 Mrad.

35

4. The composition of claim 3, wherein the dose is from about 5 to about 25 Mrad.

5. An in vivo implant comprising a crosslinked and remelted polymer.

40

6. A method for increasing the wear resistance of a preformed polymeric composition, comprising the steps of:

(a) crosslinking the polymeric composition in a solid state; and

45 (b) subjecting the crosslinked polymeric composition to thermal treatment.

50

7. The method of claim 6, further comprising the step of removing the most oxidized surface of the thermally treated crosslinked polymeric composition.

8. The method of claim 6, wherein the crosslinking is by gamma irradiation.

9. The method of claim 8, wherein the gamma irradiation is at a dose of from about 1 to about 100 Mrad.

10. The method of claim 6, wherein the thermal treatment comprises remelting the crosslinked polymer.

11. The method of claim 10, wherein the remelting temperature is between the melting temperature of the irradiated polymer to about 160°C above the melting temperature of the irradiated polymer.

12. The method of claim 6, wherein the resulting polymeric composition possesses one or more of the following characteristics: degree of swelling of between about 1.7 to about 5.3; molecular weight between crosslinks of between about 400 to about 8400 g/mol; and a gel content of between about 95 to about 99 %.

13. The method of claim 6, wherein the thermal treatment comprises annealing the crosslinked polymer.

14. The method of claim 13, wherein the annealing temperature is from about 90°C below to about 1°C below the melting temperature of the irradiated polymer.

15. A polymeric composition made from the steps of:
(a) crosslinking a starting polymer in a solid state to form a crosslinked polymer; and
(b) subjecting the crosslinked polymer to thermal treatment.

16. The polymeric composition of claim 15, further comprising the step of removing the most oxidized surface of the crosslinked polymeric composition.

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17. The polymeric composition of claim 15, wherein the
20 crosslinking is by gamma irradiation.

18. The polymeric composition of claim 17, wherein the
gamma irradiation is at a dose of from about 1 to about 100
Mrad.

25 19. The polymeric composition of claim 15, wherein the
thermal treatment comprises remelting the crosslinked poly-
mer.

30 20. The polymeric composition of claim 19, wherein the
remelting temperature is between the melting temperature of
the irradiated polymer to about 160°C above the melting
temperature of the irradiated polymer.

35 21. The polymeric composition of claim 15, wherein the
thermal treatment comprises annealing the crosslinked poly-
mer.

40 22. The method of claim 21, wherein the annealing
temperature is between about 90°C below to about 1°C below
the melting temperature of the irradiated polymer.

45 23. A product made by the process of:
(a) crosslinking a preformed polymeric composition in
a solid state;
(b) subjecting the crosslinked polymeric composition
to thermal treatment; and
(c) fashioning the product from the crosslinked poly-
meric composition.

50 24. The product of claim 23, further comprising the
step of removing the most oxidized surface of the
crosslinked polymer.

20

25. The product of claim 24, wherein the product is an
in vivo implant.

25

26. A method for determining an optimal radiation dose and thermal treatment for treating a polymer to increase its wear resistance, when made into a desired product, while maintaining its desirable physical and/or chemical properties, the method comprises the steps of:

30

(a) irradiating the polymer in the solid state over a range of radiation doses likely to produce the desirable wear resistance and physical and/or chemical properties;

35

(b) remelting the polymer;

(c) correlating the radiation doses with the wear rate of the desired product made from the irradiated remelted polymer using actual or simulated wear conditions for the desired product;

40

(d) correlating the radiation doses with each of the physical and/or chemical properties of the desired product made from the irradiated remelted polymer using actual or simulated wear conditions for the desired product;

45

(e) comparing the correlations in steps (c) and (d) to determine the optimal radiation dose which will produce a desirable wear rate while maintaining the desirable physical and/or chemical properties, if such a radiation dose is arrived at, use this optimal radiation dose for future treatment of the polymer;

50

(f) if the optimal radiation dose cannot be arrived at in step (e), then determining a dose that would produce a desirable wear rate based on the correlation of step (c) and annealing instead of remelting the polymer which has been irradiated to said dose;

55

(g) correlating the physical and/or chemical properties of the desired product made from the irradiated and annealed polymer, using actual or simulated wear conditions

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20 for the desired product, with different annealing times and temperatures;

(h) determining an annealing temperature and time which will provide the desirable wear rate and physical and/or chemical properties, if this is possible, then use the radiation dose and annealing conditions determined at this step for future treatment of the polymer;

25 (i) if step (h) does not provide the desirable wear rate and physical and/or chemical properties, then apply a lower radiation dose and repeat steps (c) to (i) or (h) until the optimal radiation dose and annealing conditions are determined or the steps confirm that no optimal radiation dose and annealing conditions can be obtained for the desired wear rate and physical and/or chemical properties.

30 27. The method of claim 26, wherein the irradiation is gamma irradiation between a range of about 1 to 100 Mrad; the remelting temperature is between the melting temperature of the irradiated polymer to about 160°C above the melting temperature of the irradiated polymer; and the annealing temperature is between about 90°C below to about 1°C below the melting temperature of the irradiated polymer.

40 28. A polymer produced by irradiation and thermal treatment, wherein the radiation dose and remelting or annealing conditions are determinable by the method of claim 27.

45 29. An in vivo implant made from the polymer of claim 26, wherein the most oxidized surface of the polymer is removed.

50 30. A process for treating a polymer, wherein the process employs radiation dose and remelting or annealing conditions determinable by the steps of claim 26.

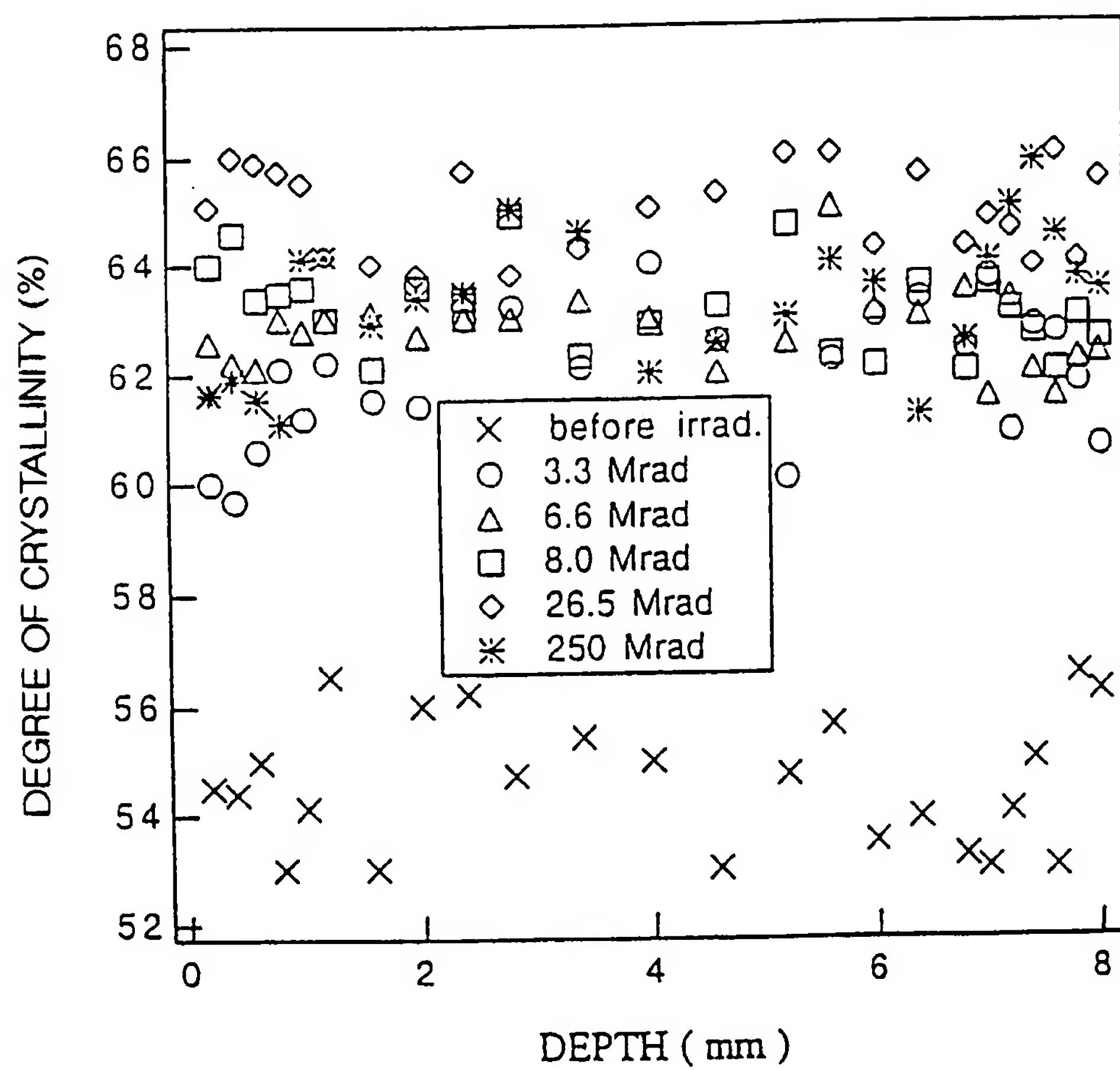


FIG. 1

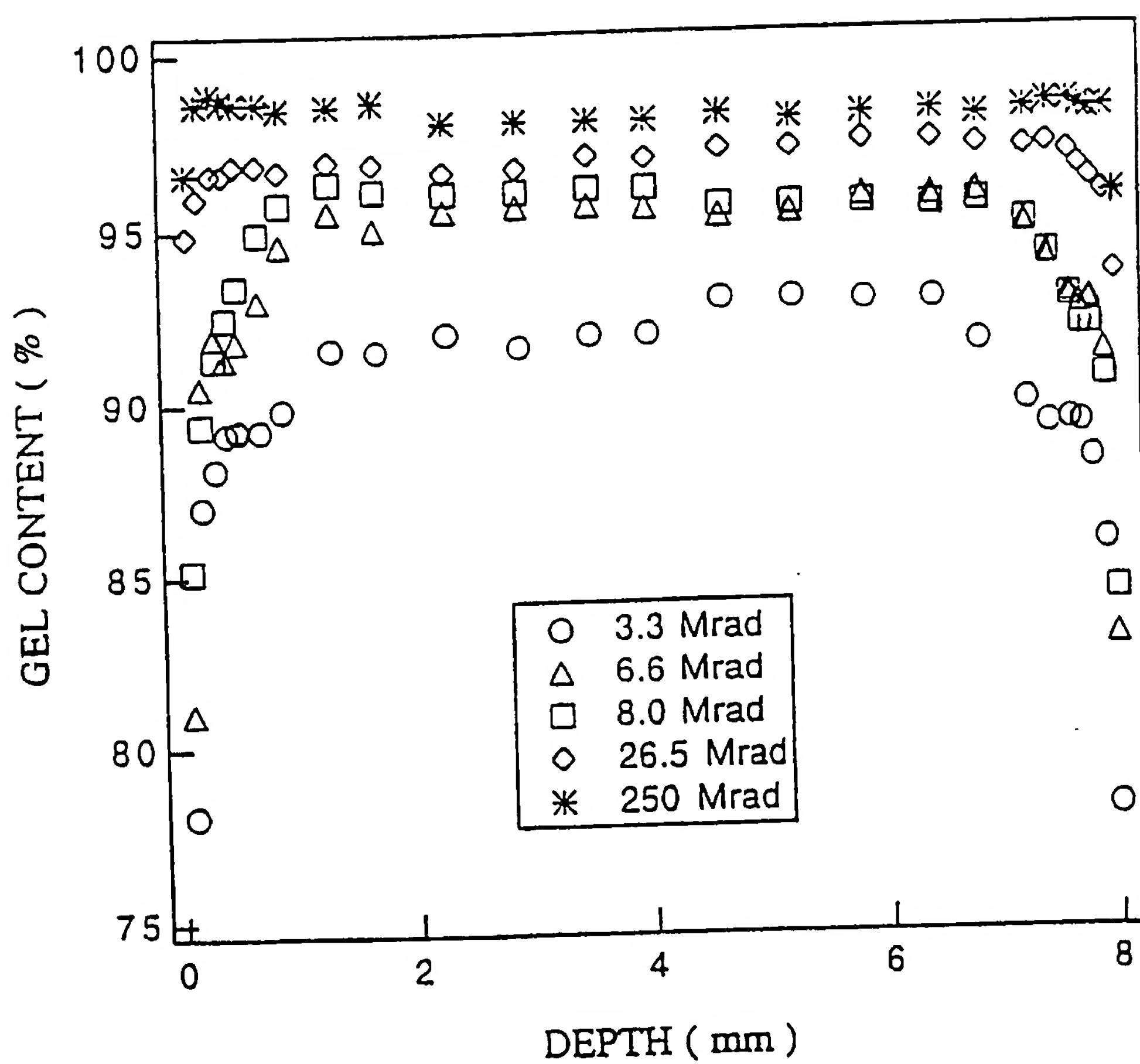


FIG. 2

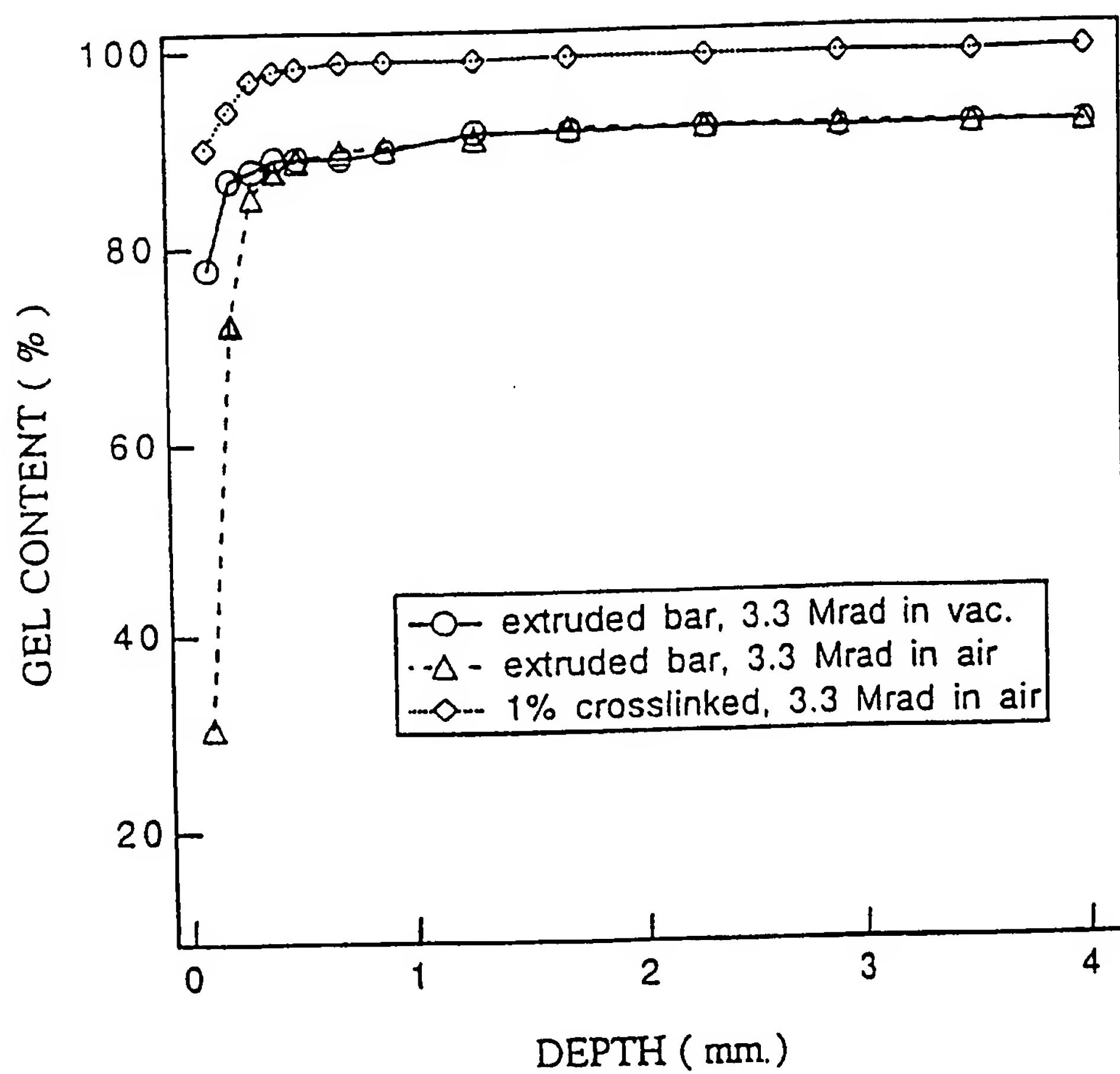


FIG. 3

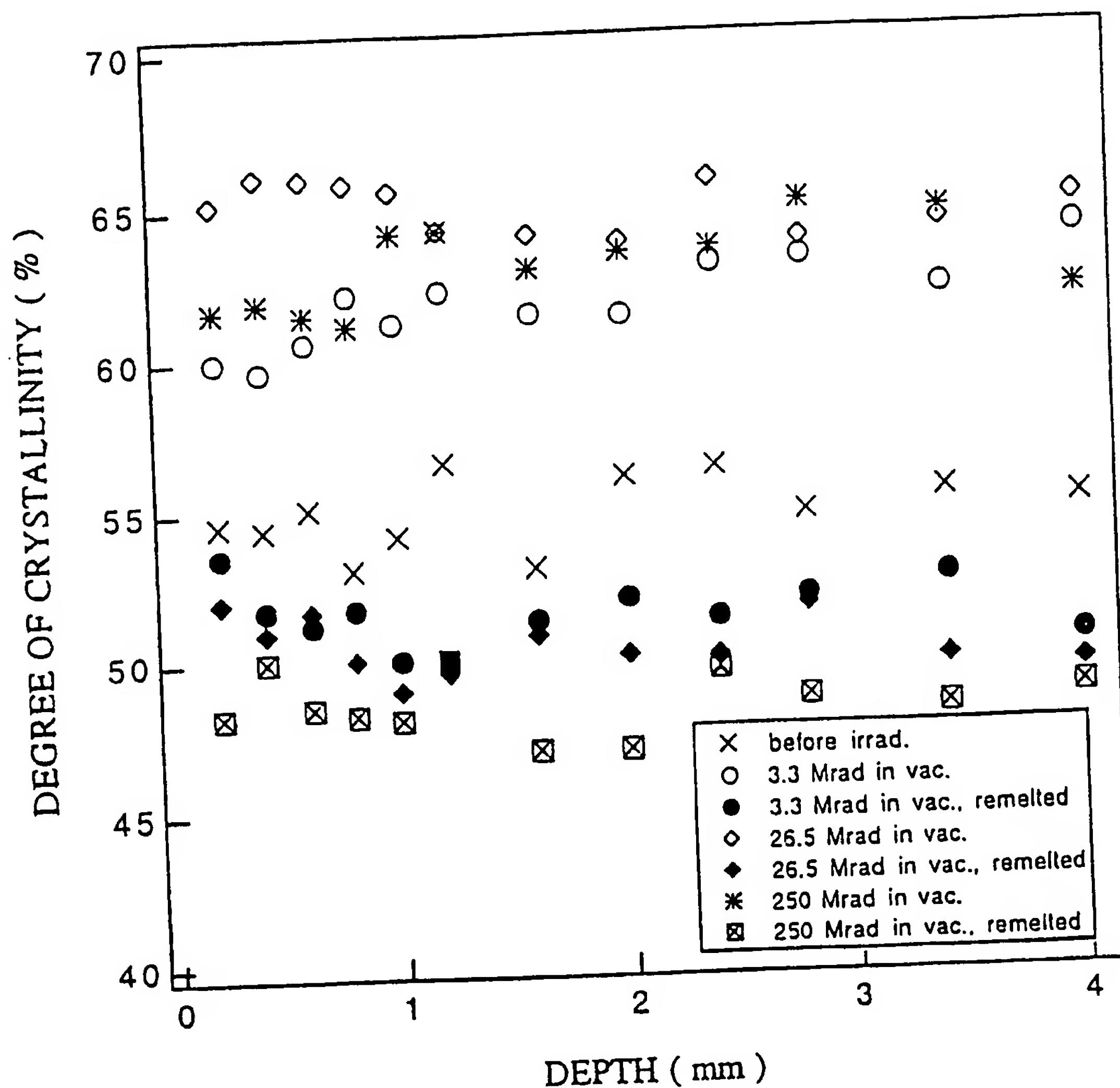


FIG. 4

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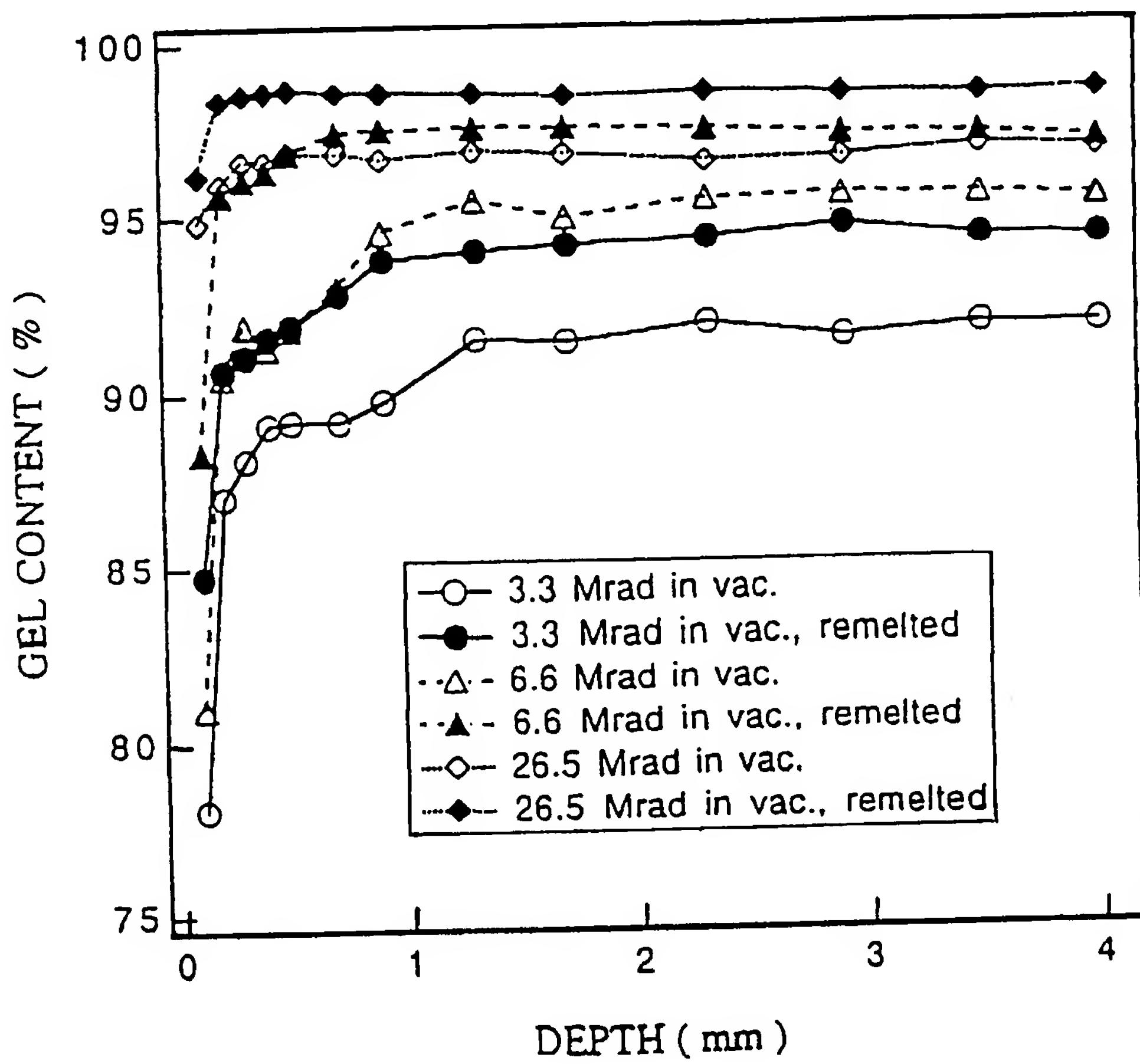
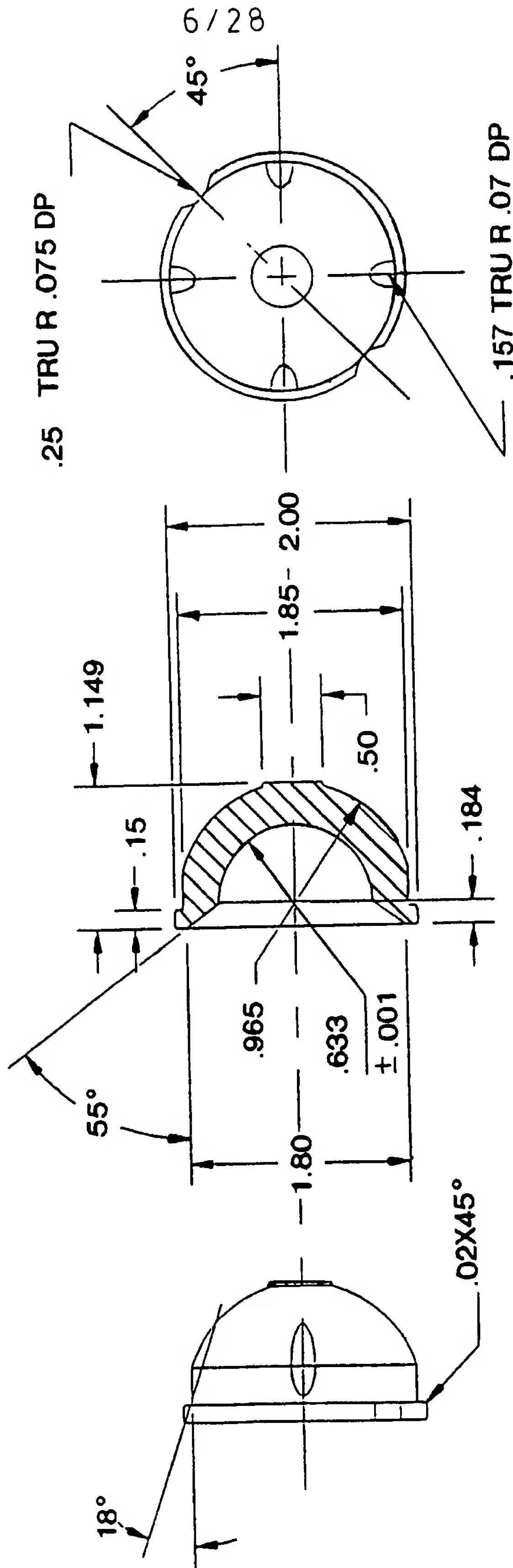
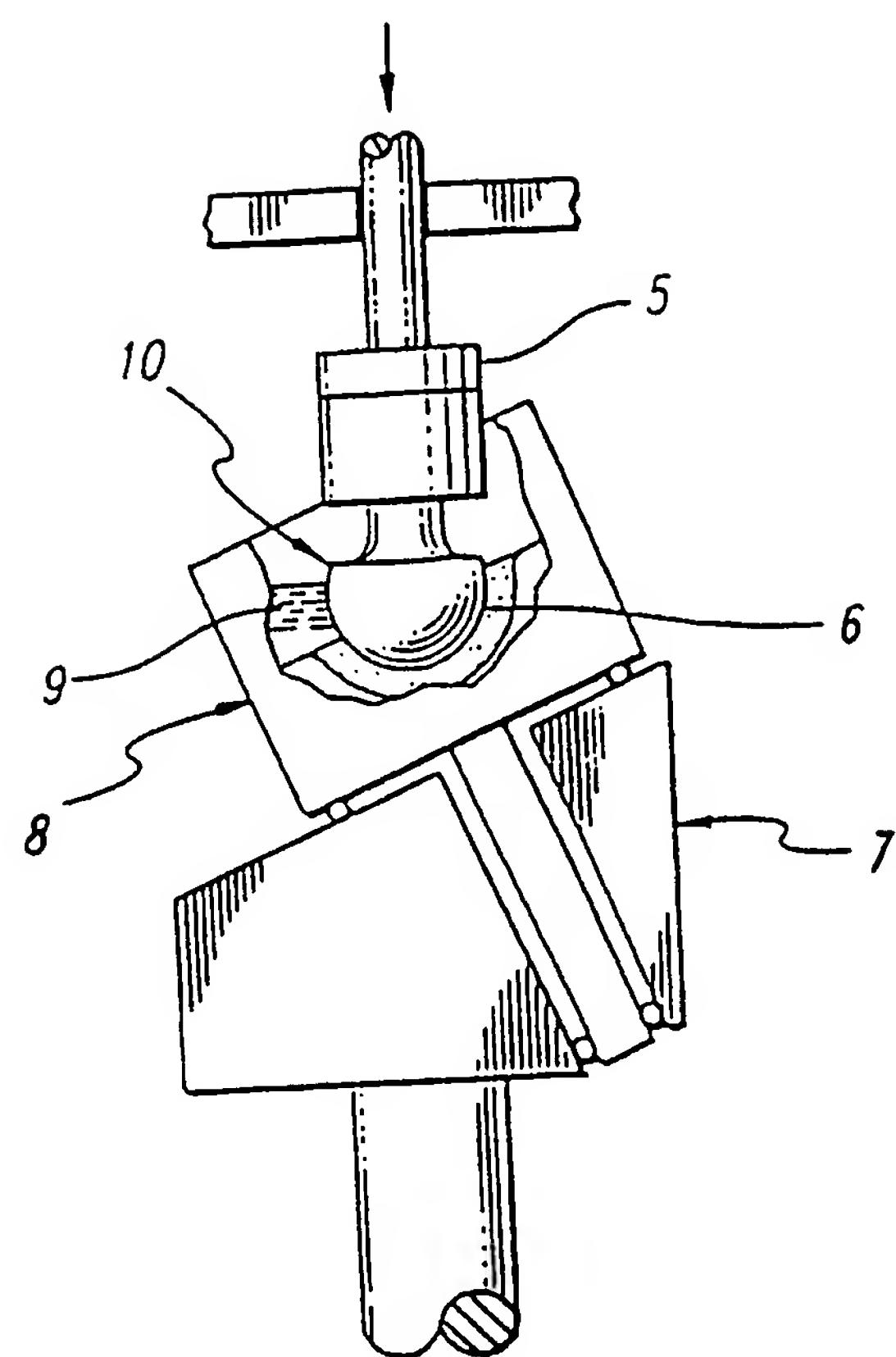


FIG. 5

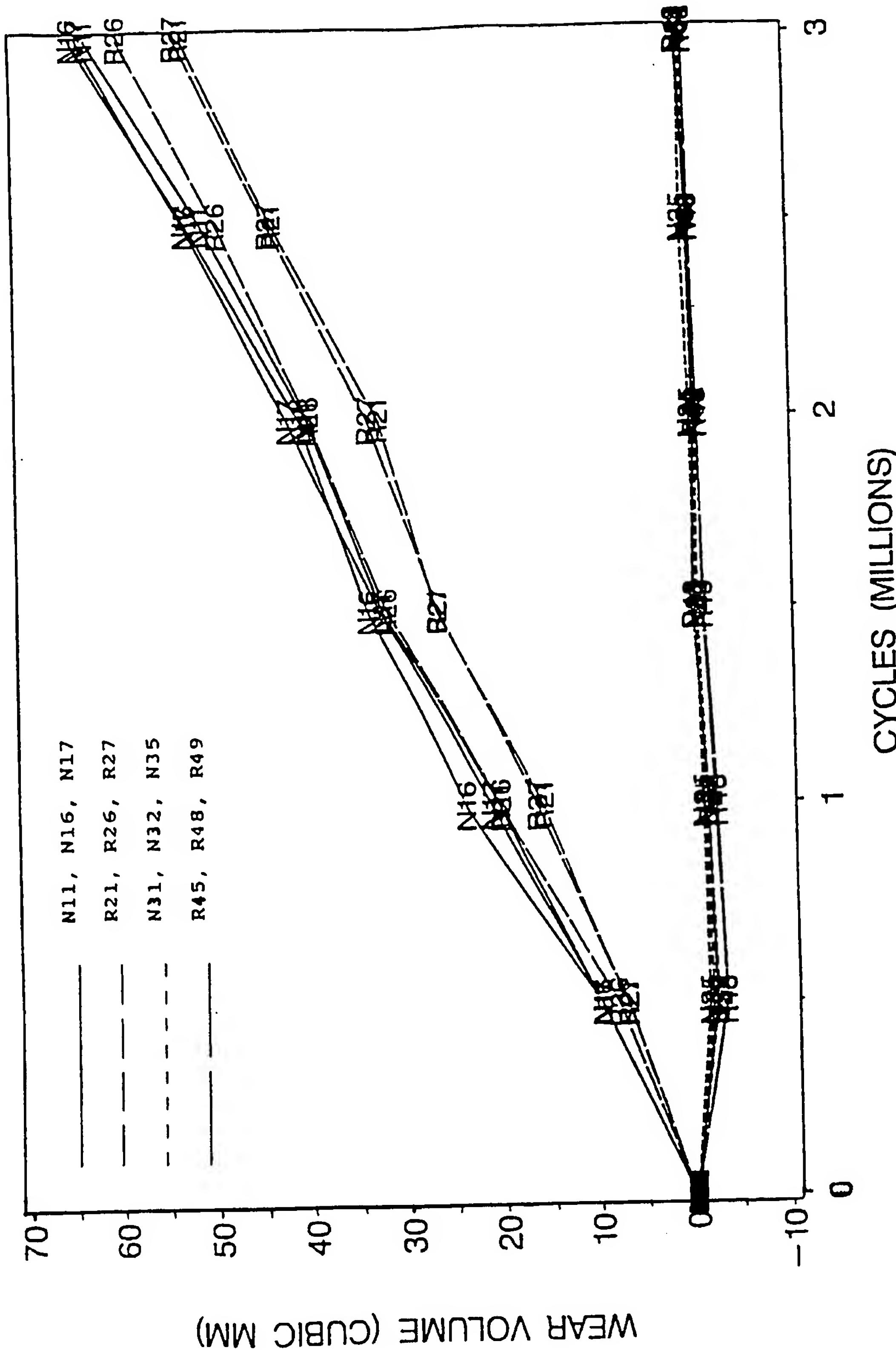
FIG. 6



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**FIG. 7**

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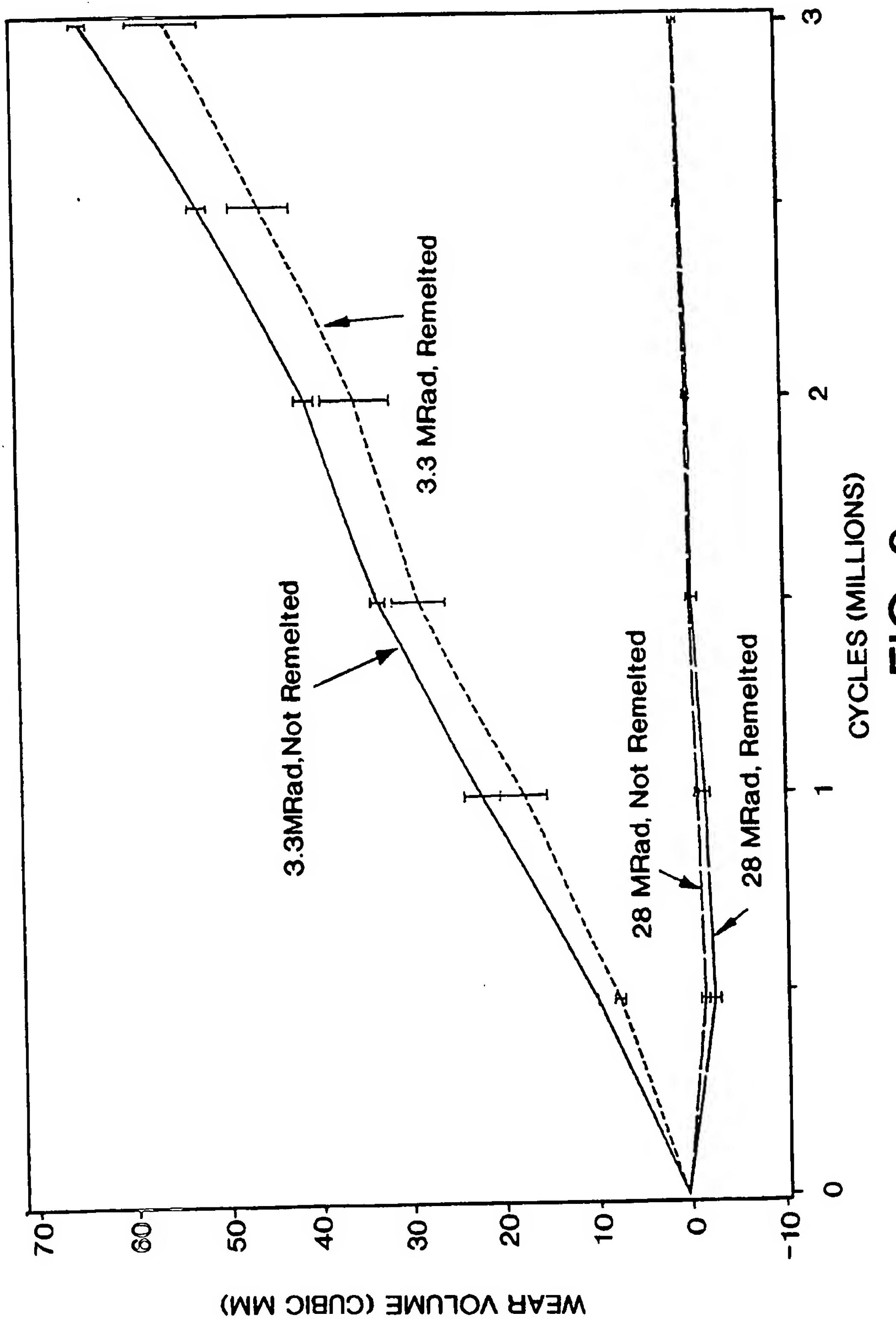
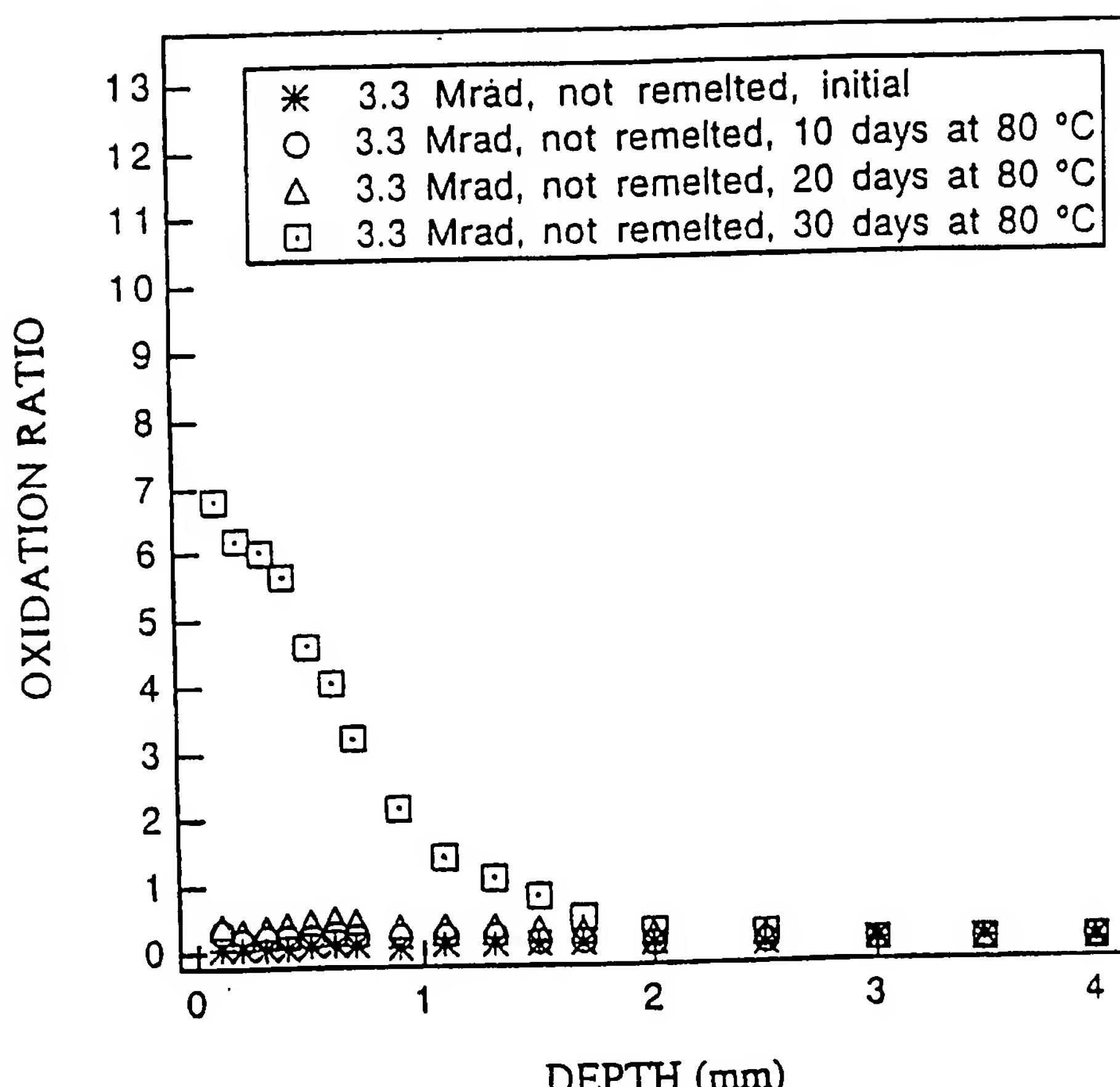


FIG. 9

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**FIG. 10**

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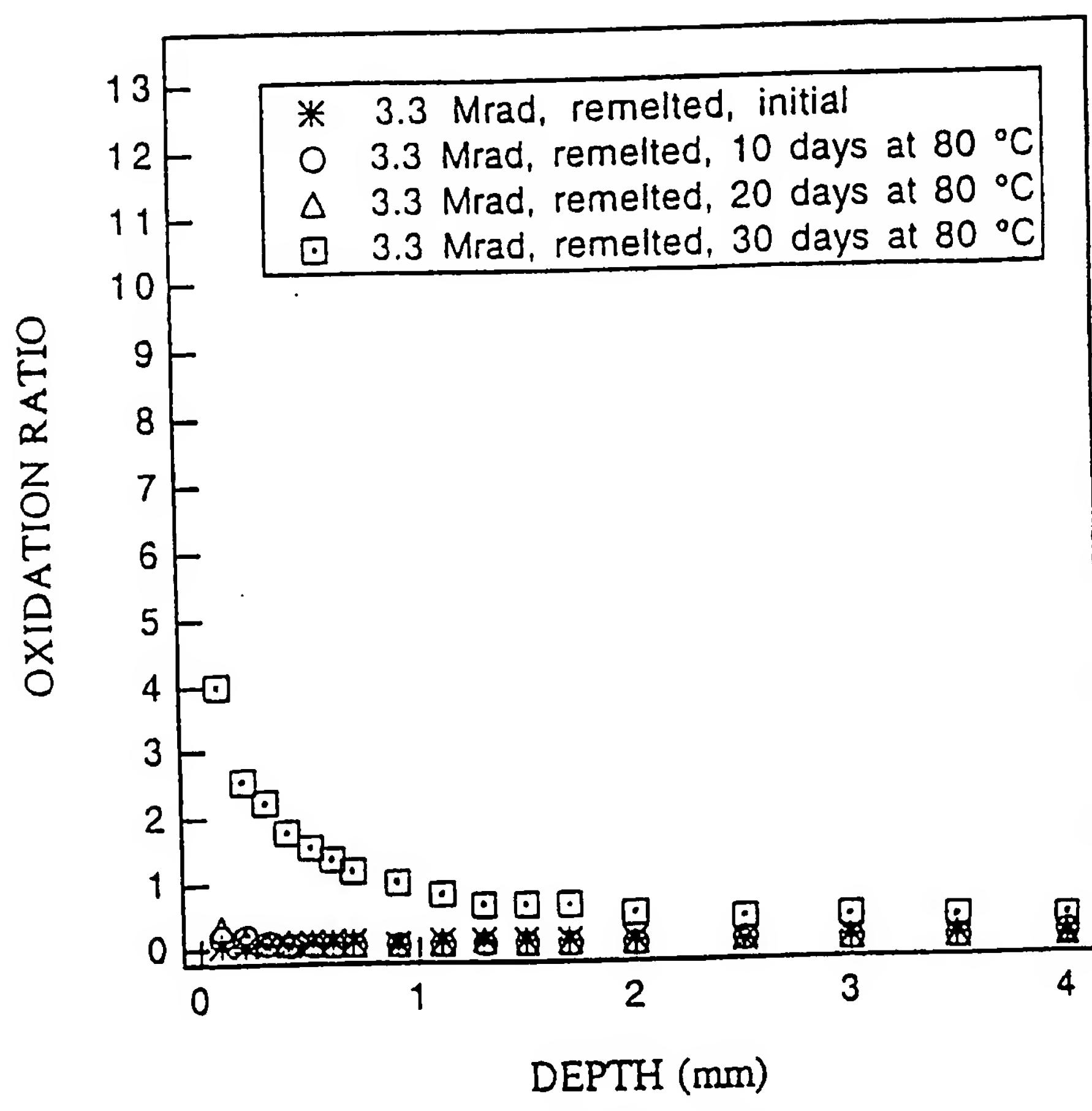


FIG. 11

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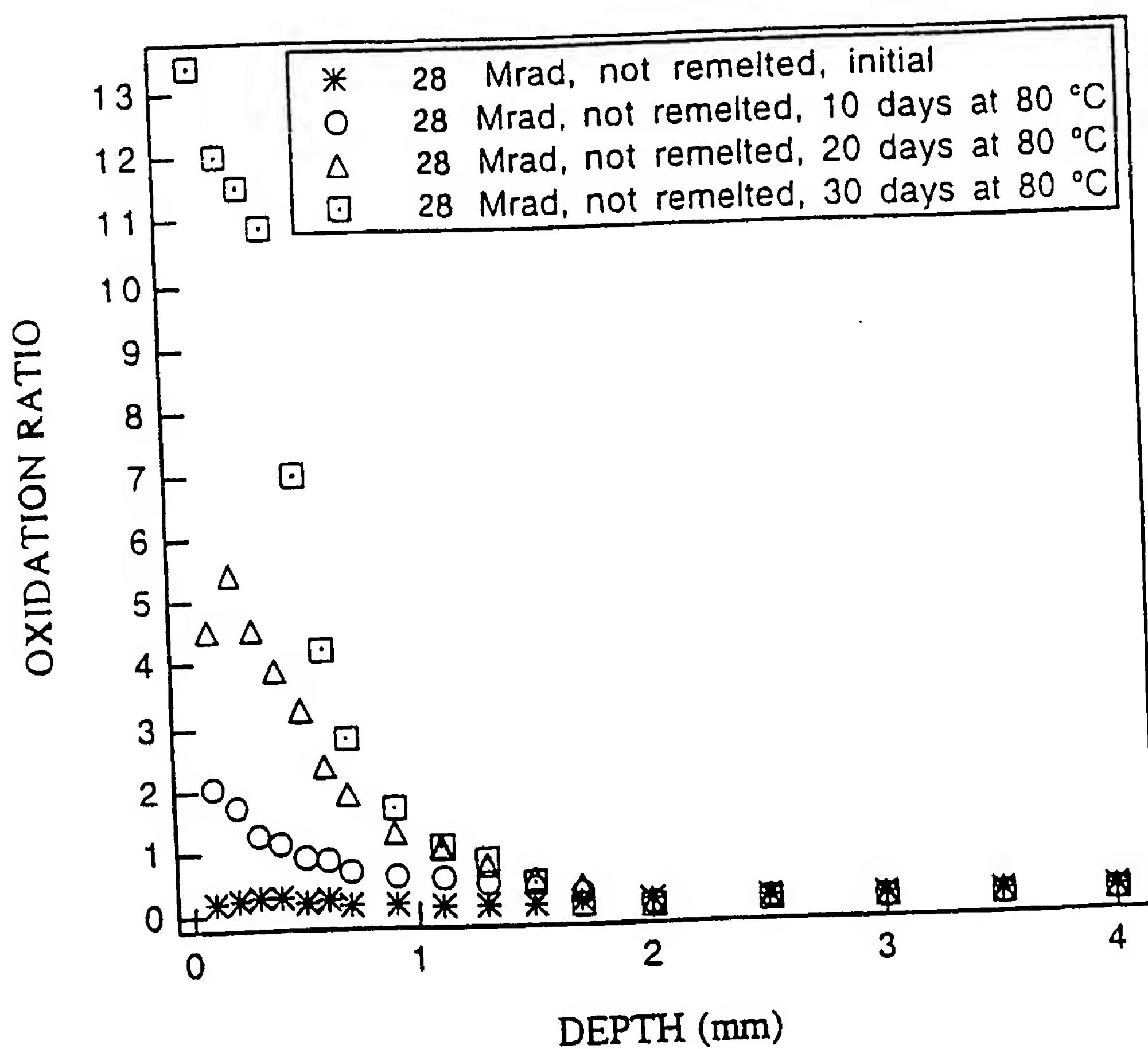


FIG. 12

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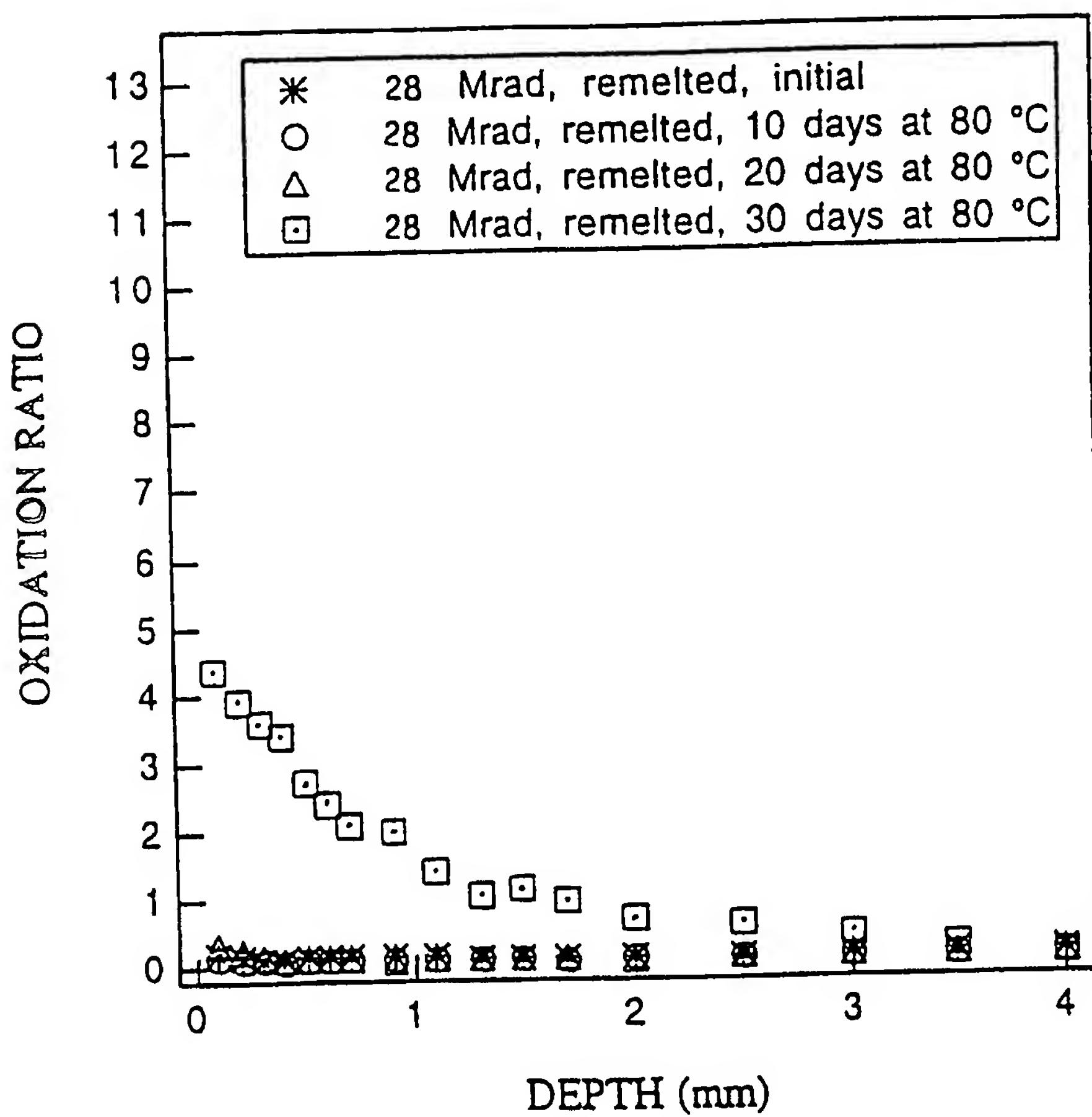


FIG. 13

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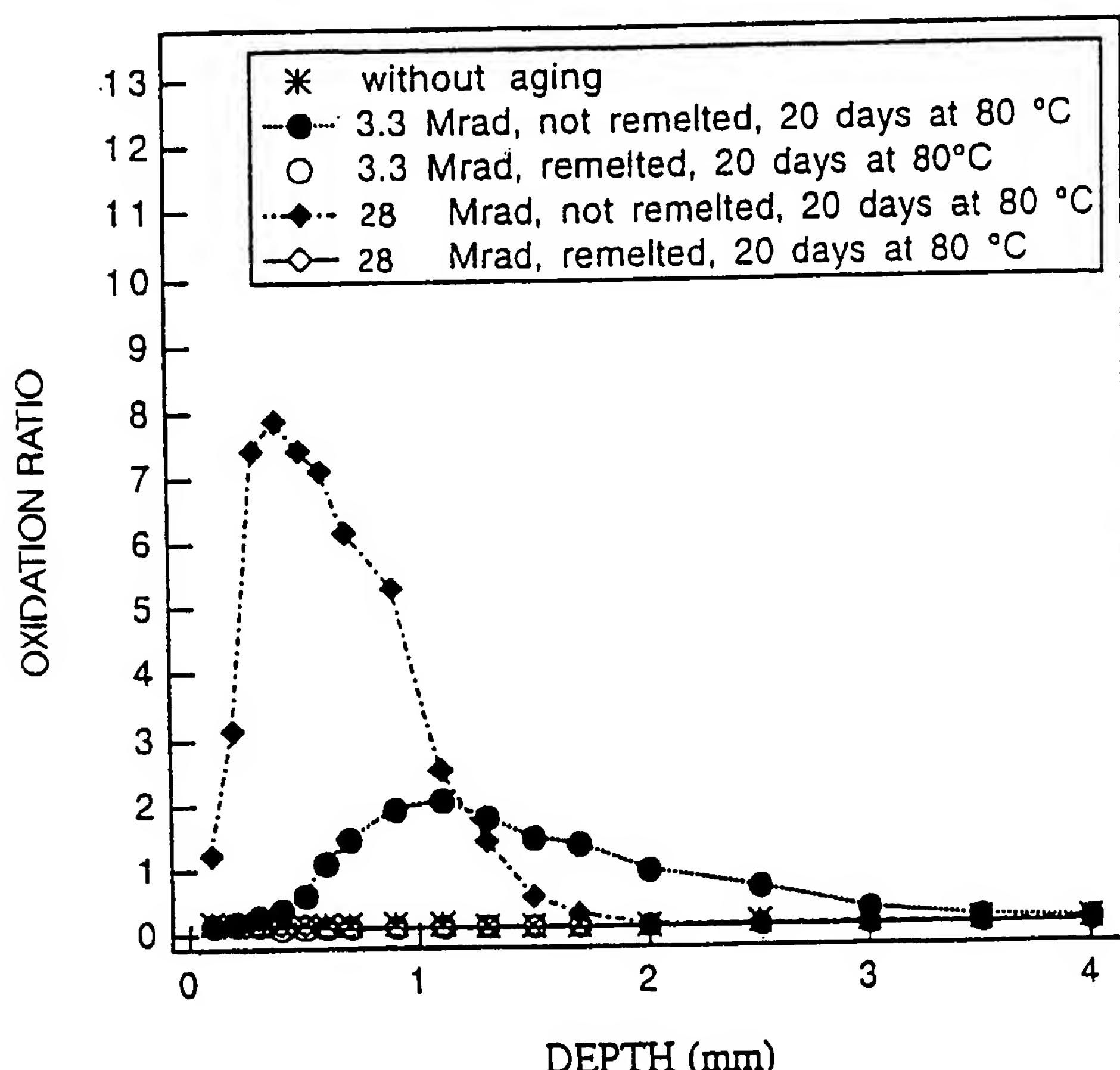


FIG. 14

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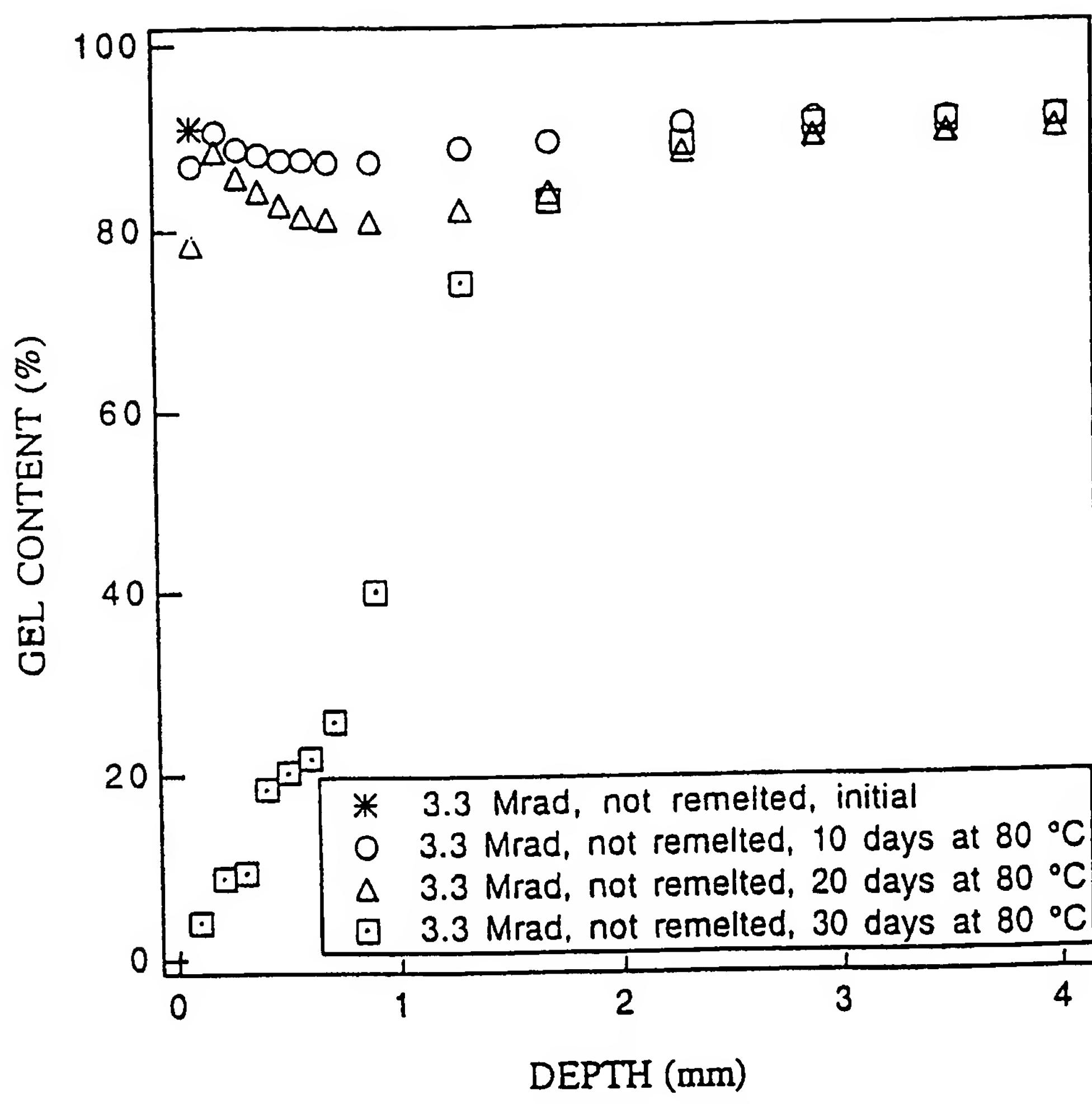


FIG. 15

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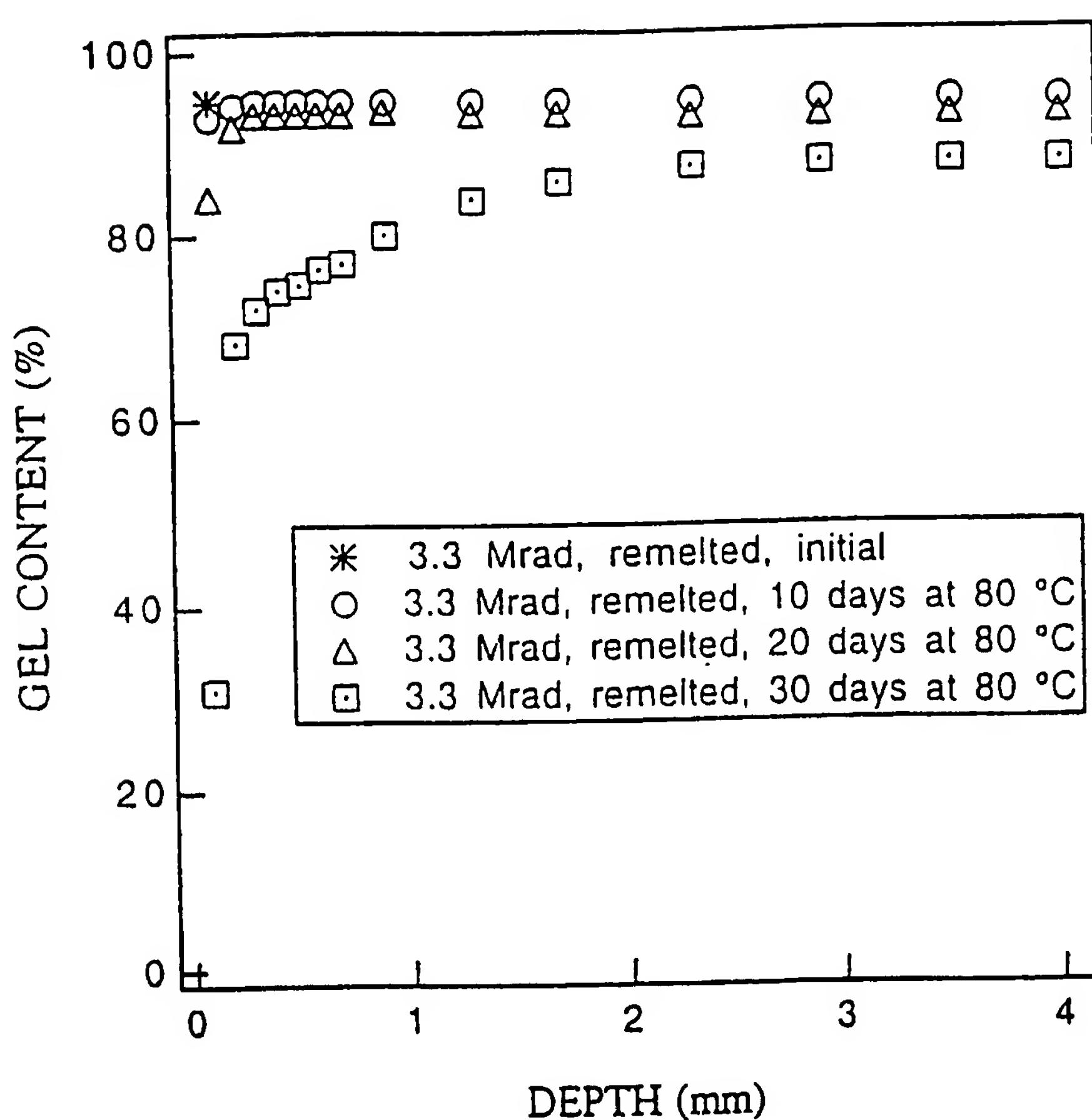


FIG. 16

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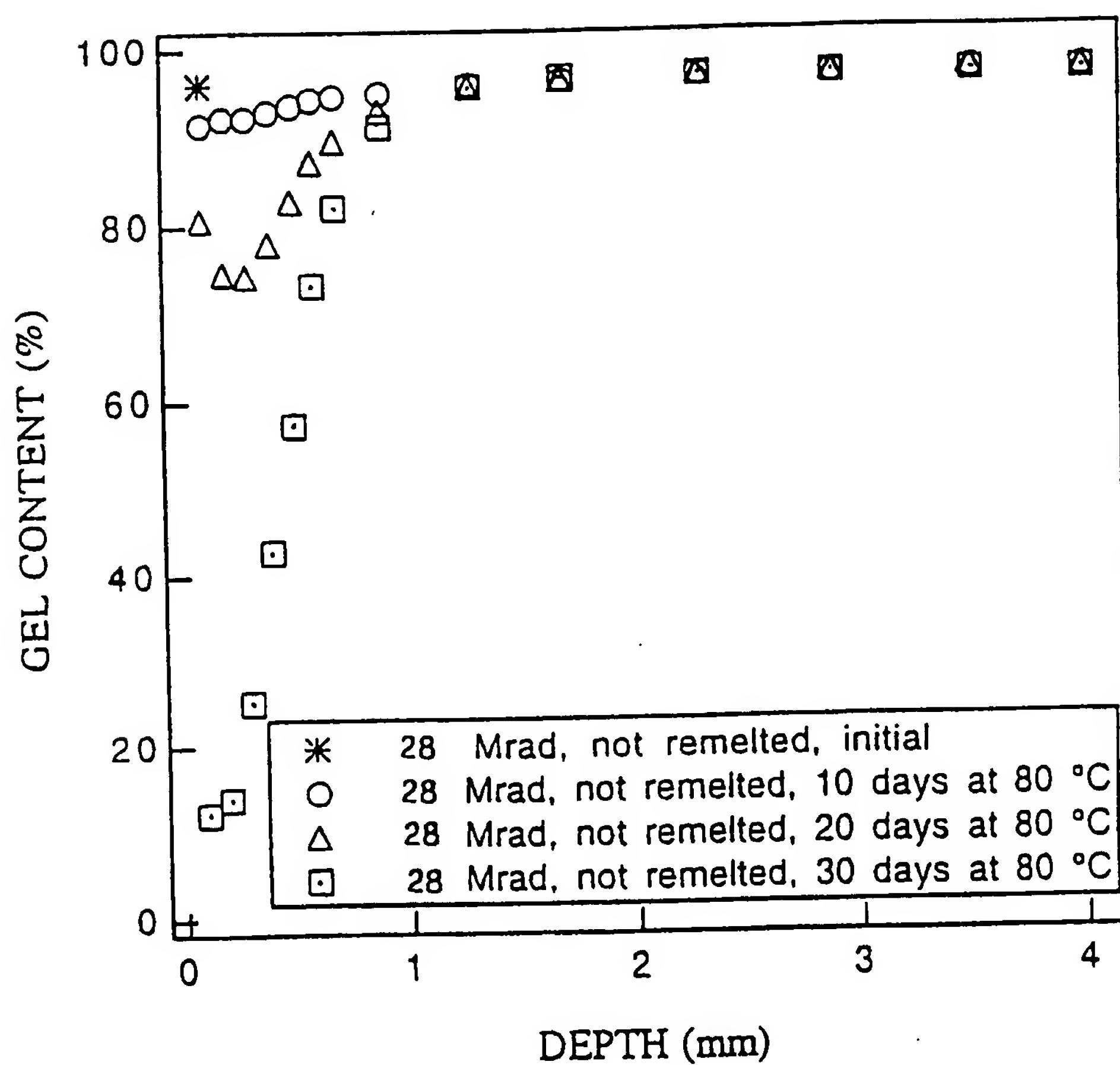


FIG. 17

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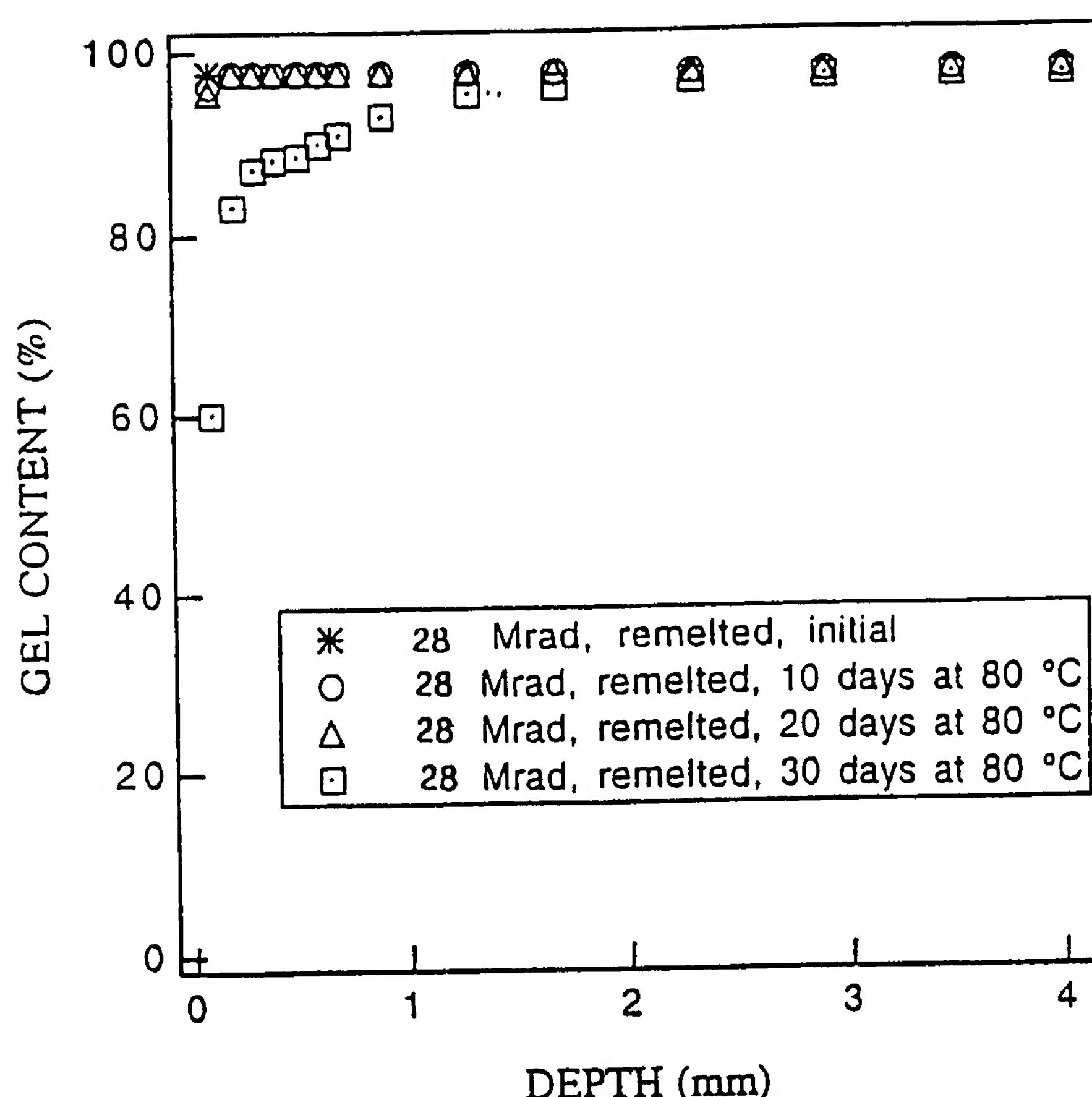


FIG. 18

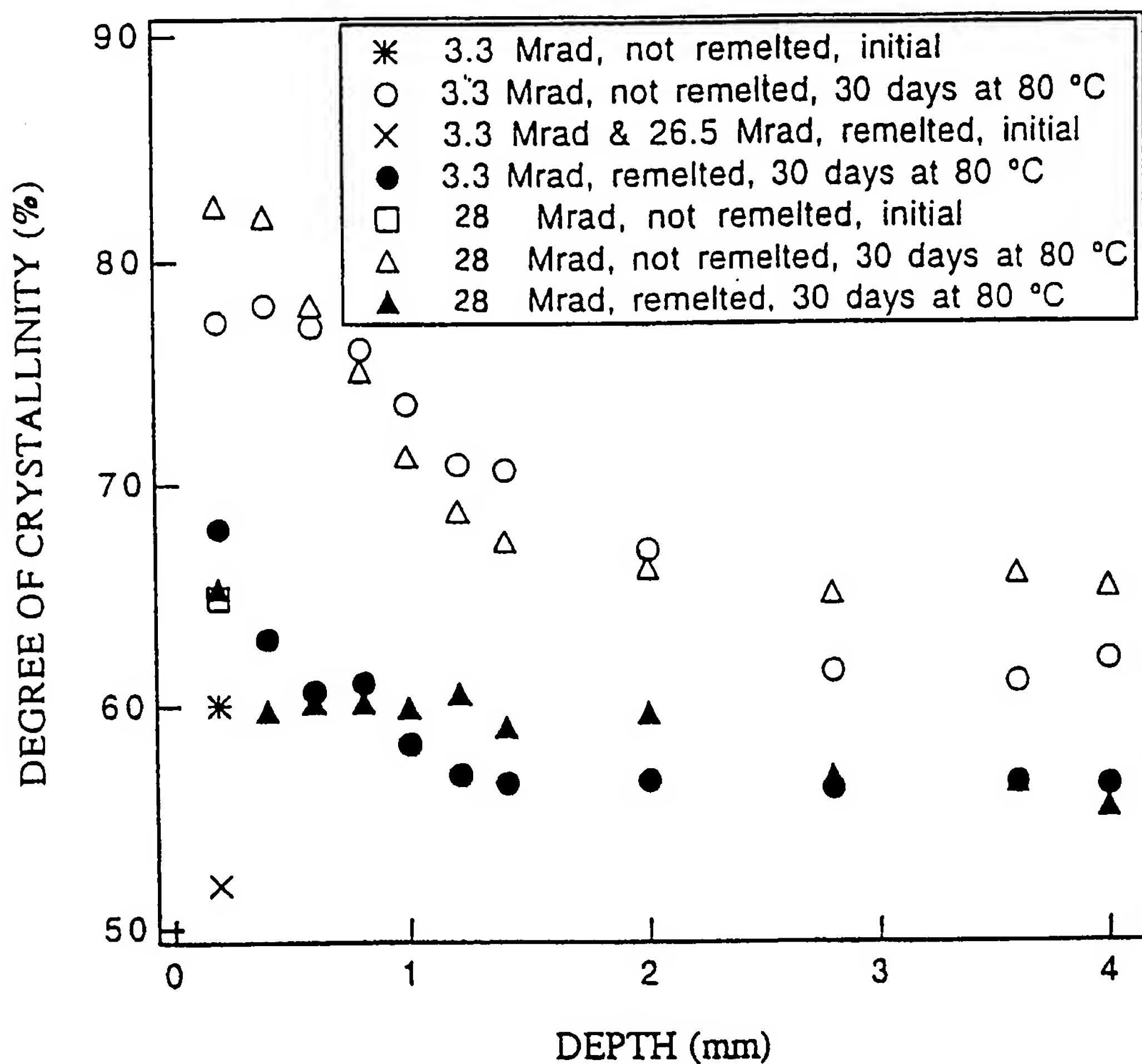


FIG. 19

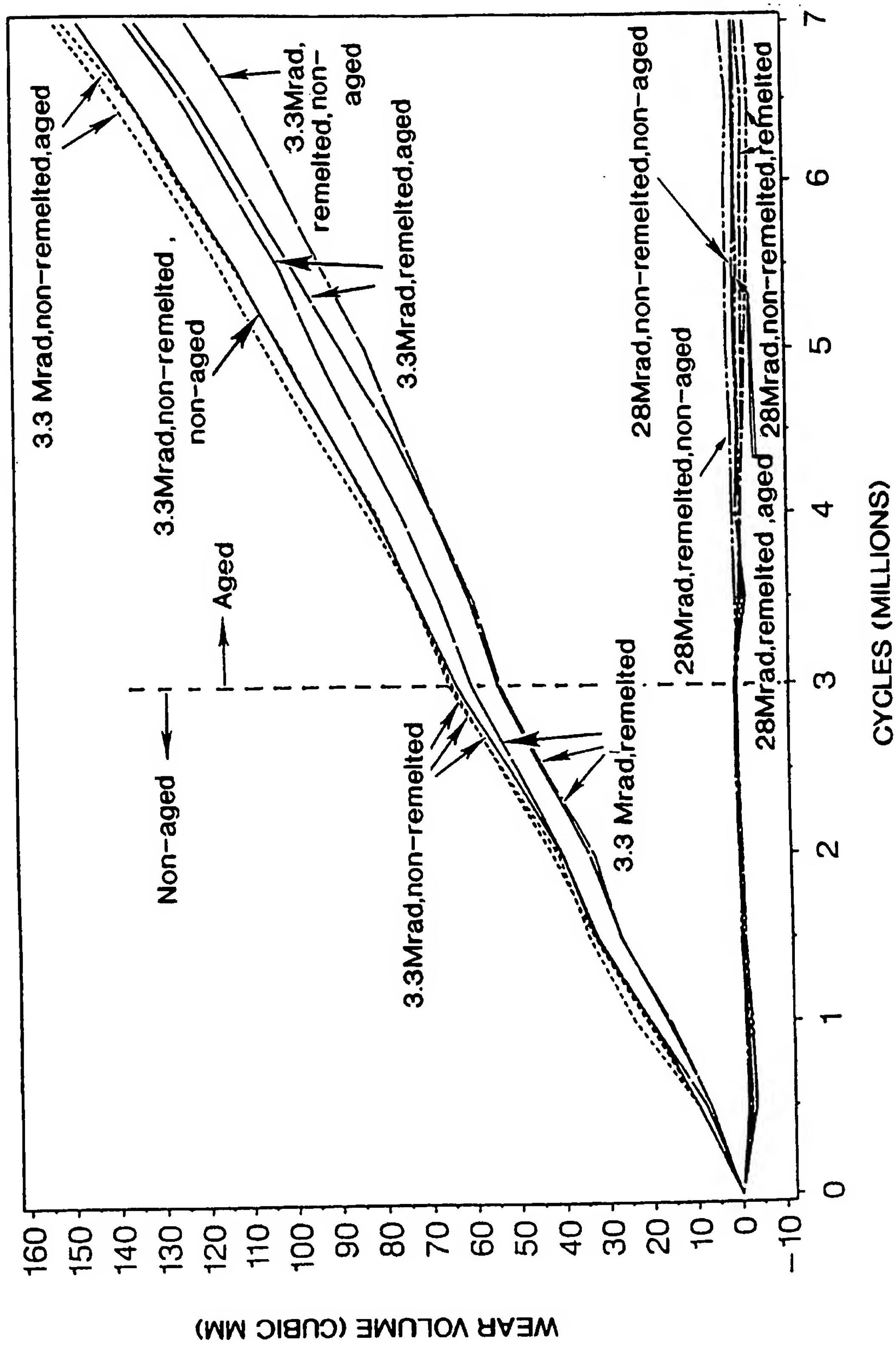


FIG. 20

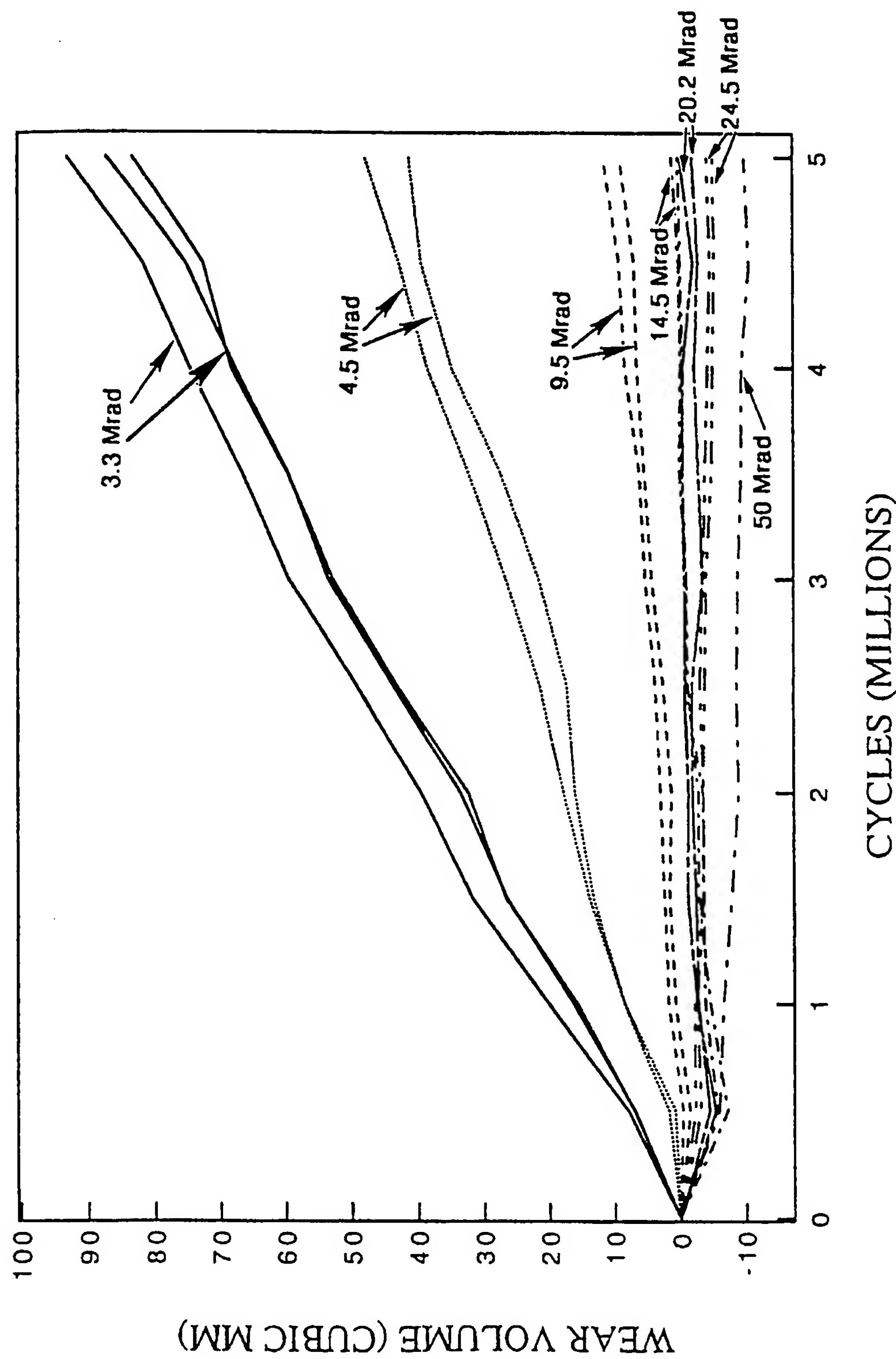


FIG. 21

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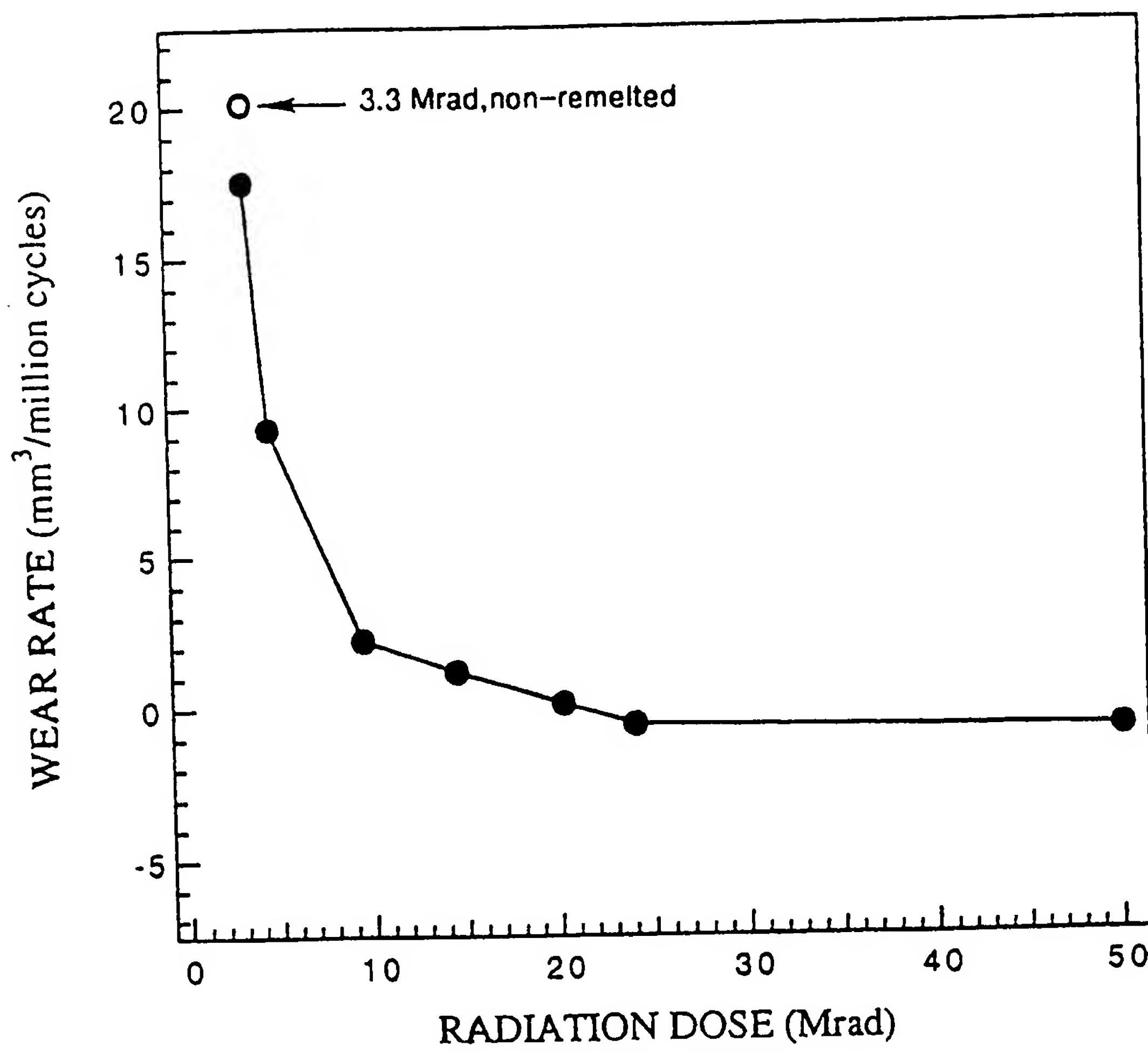


FIG. 22

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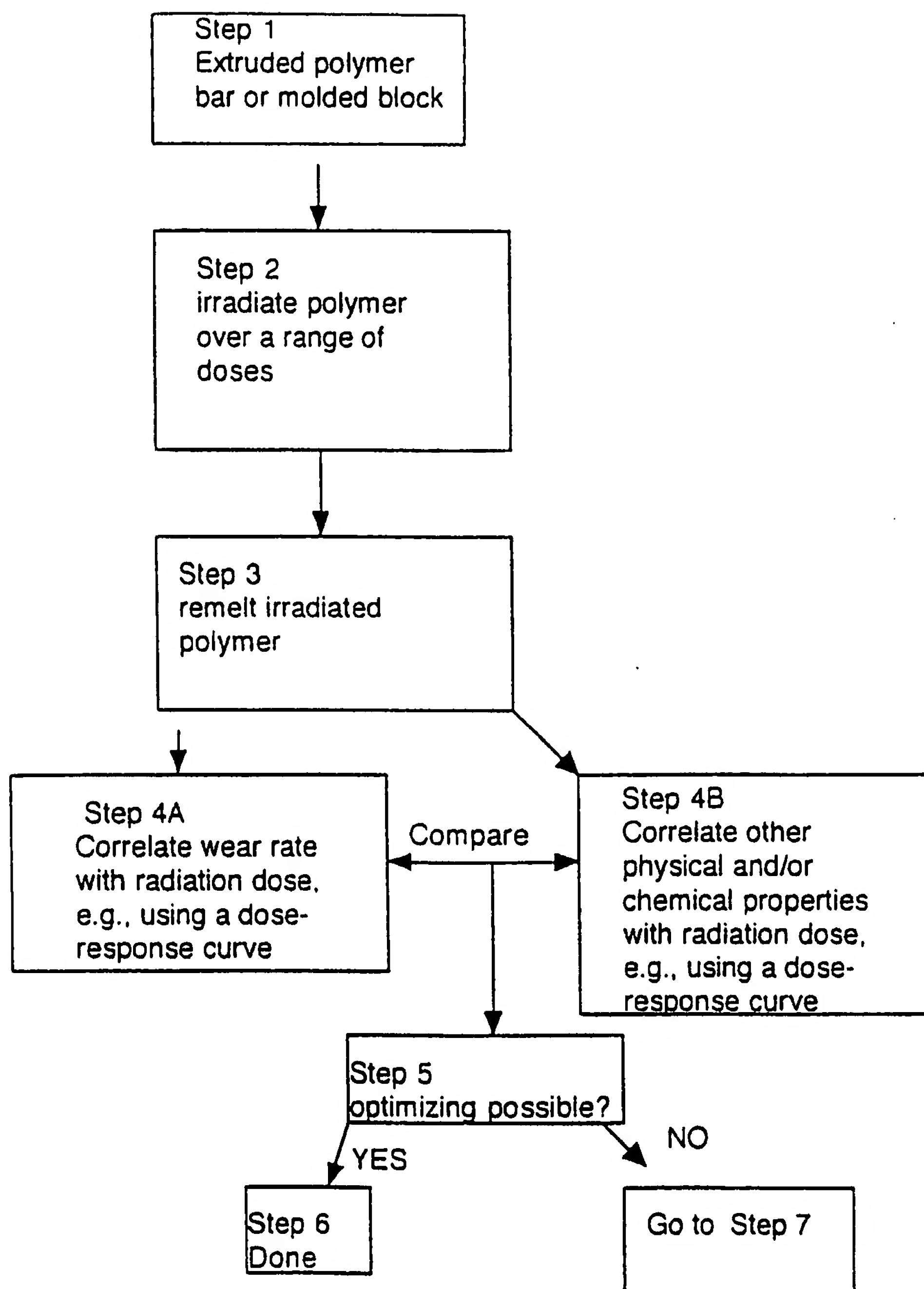


FIG. 23A

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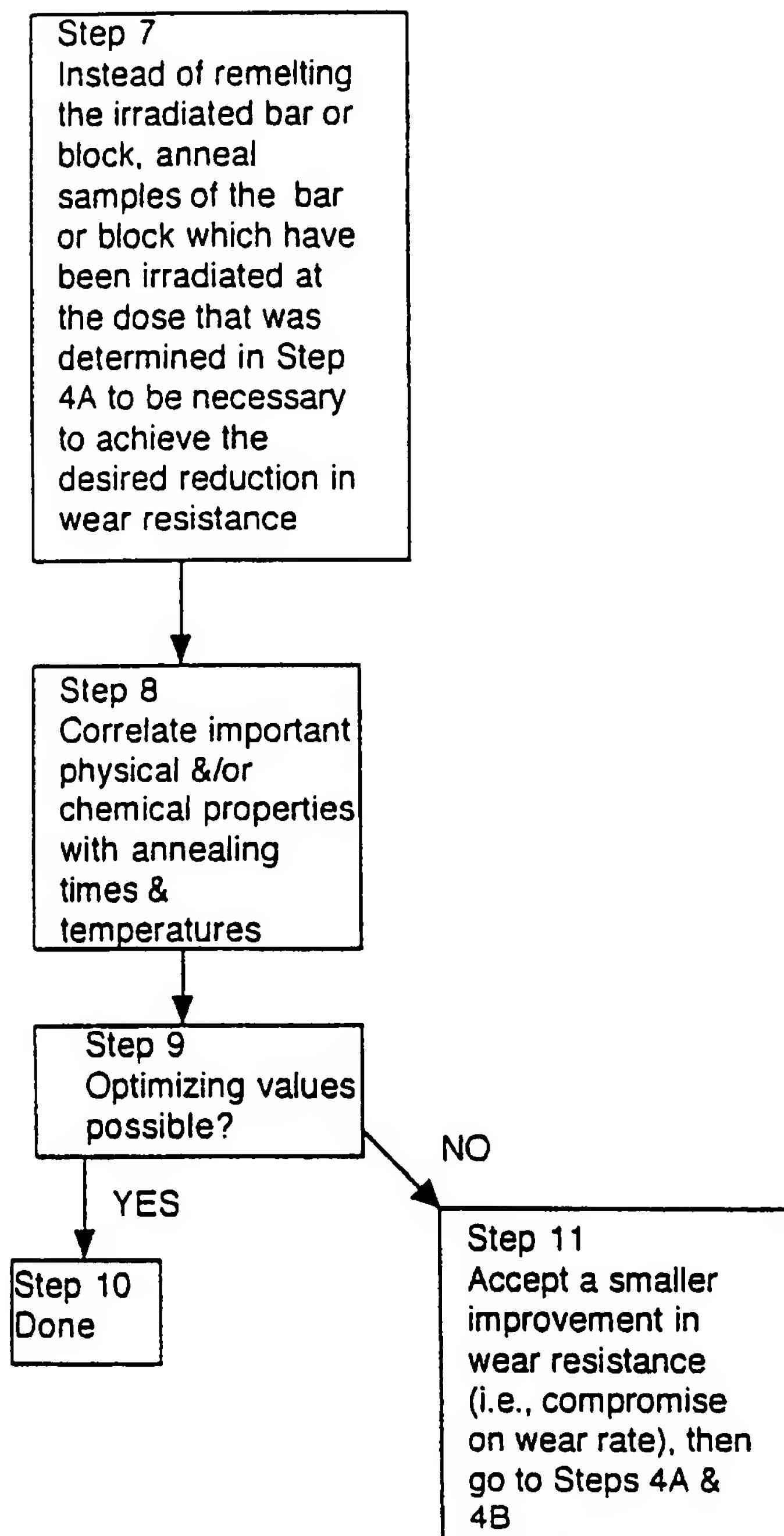


FIG. 23B

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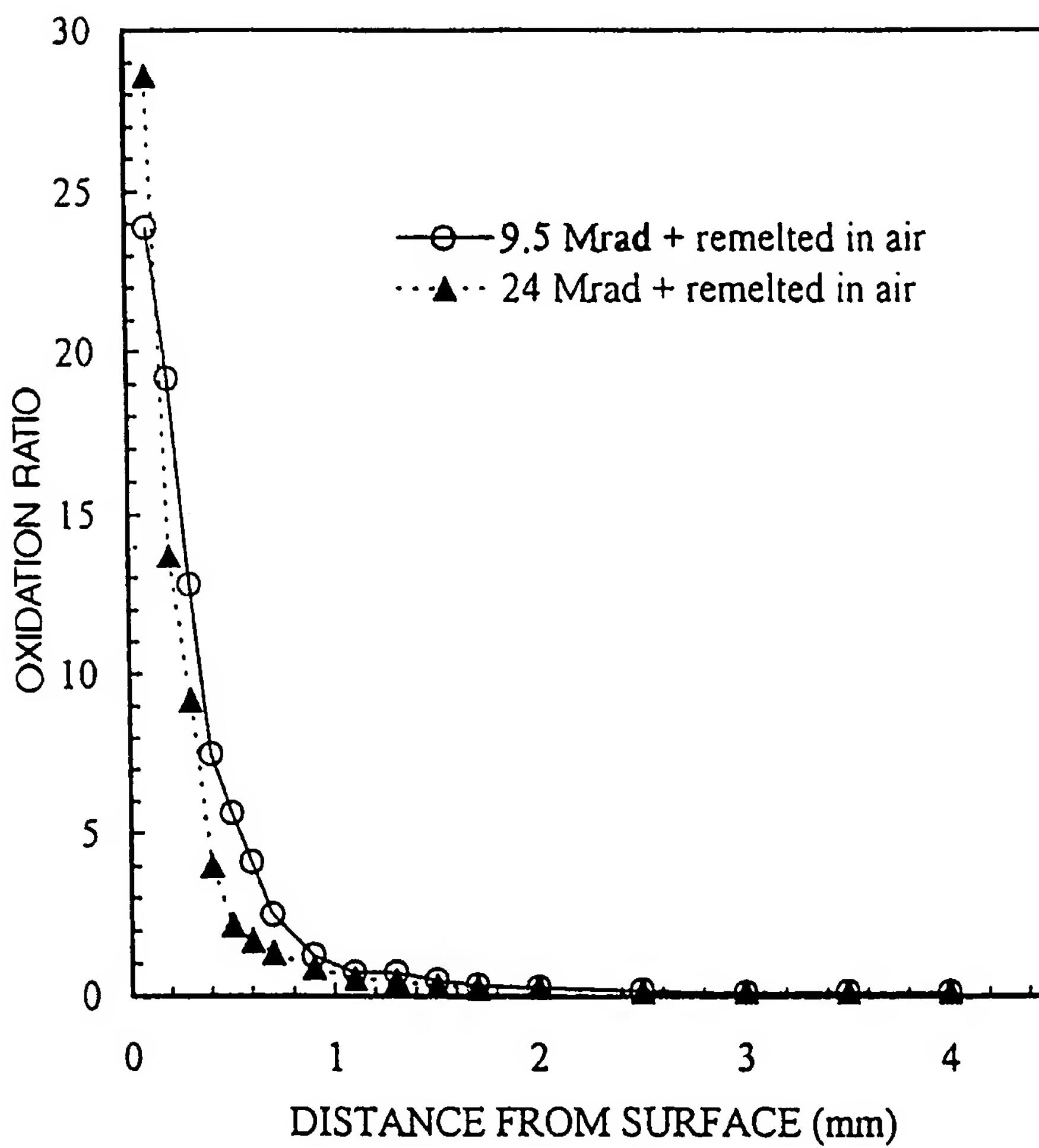


FIG. 24

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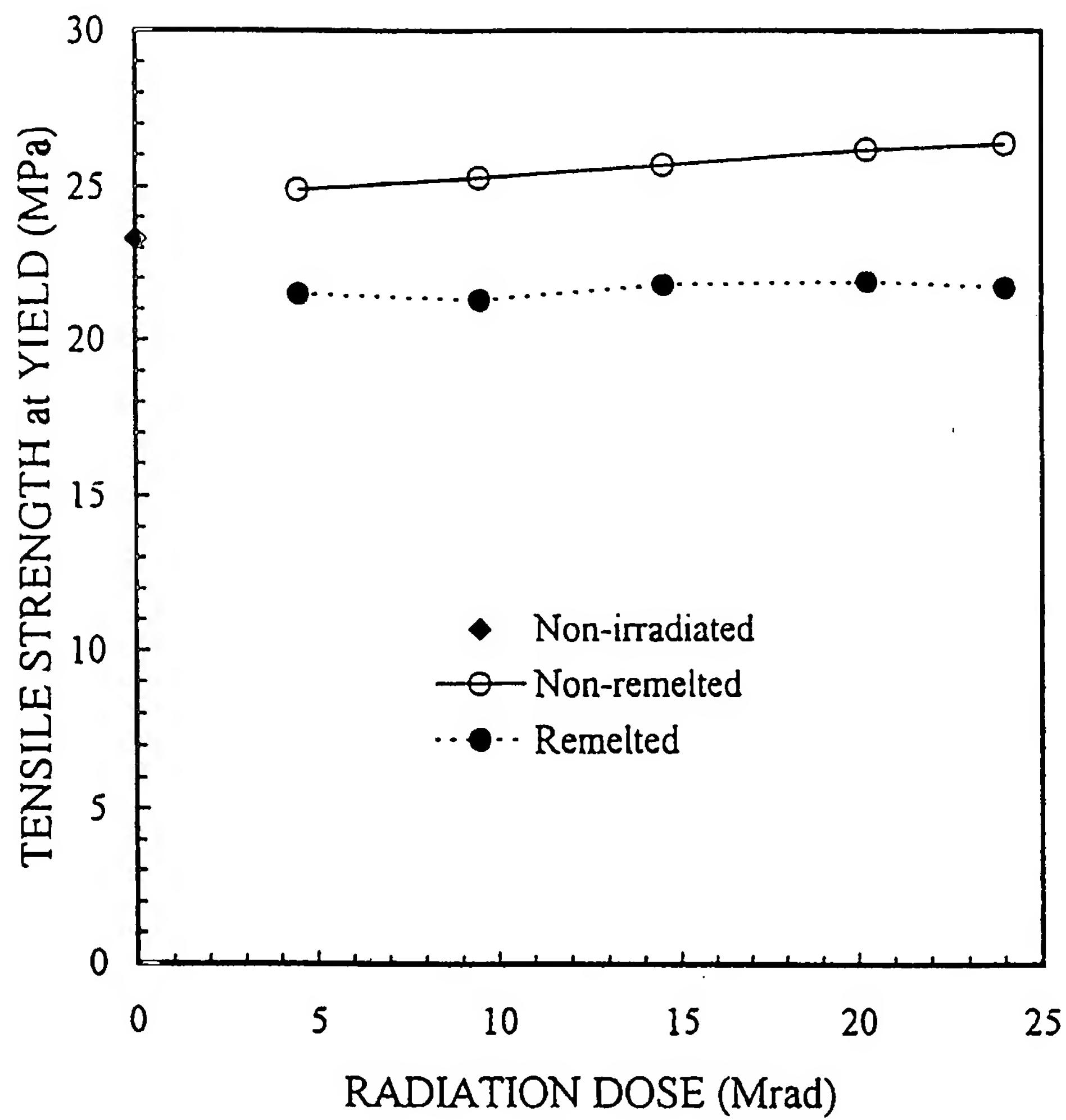


FIG. 25

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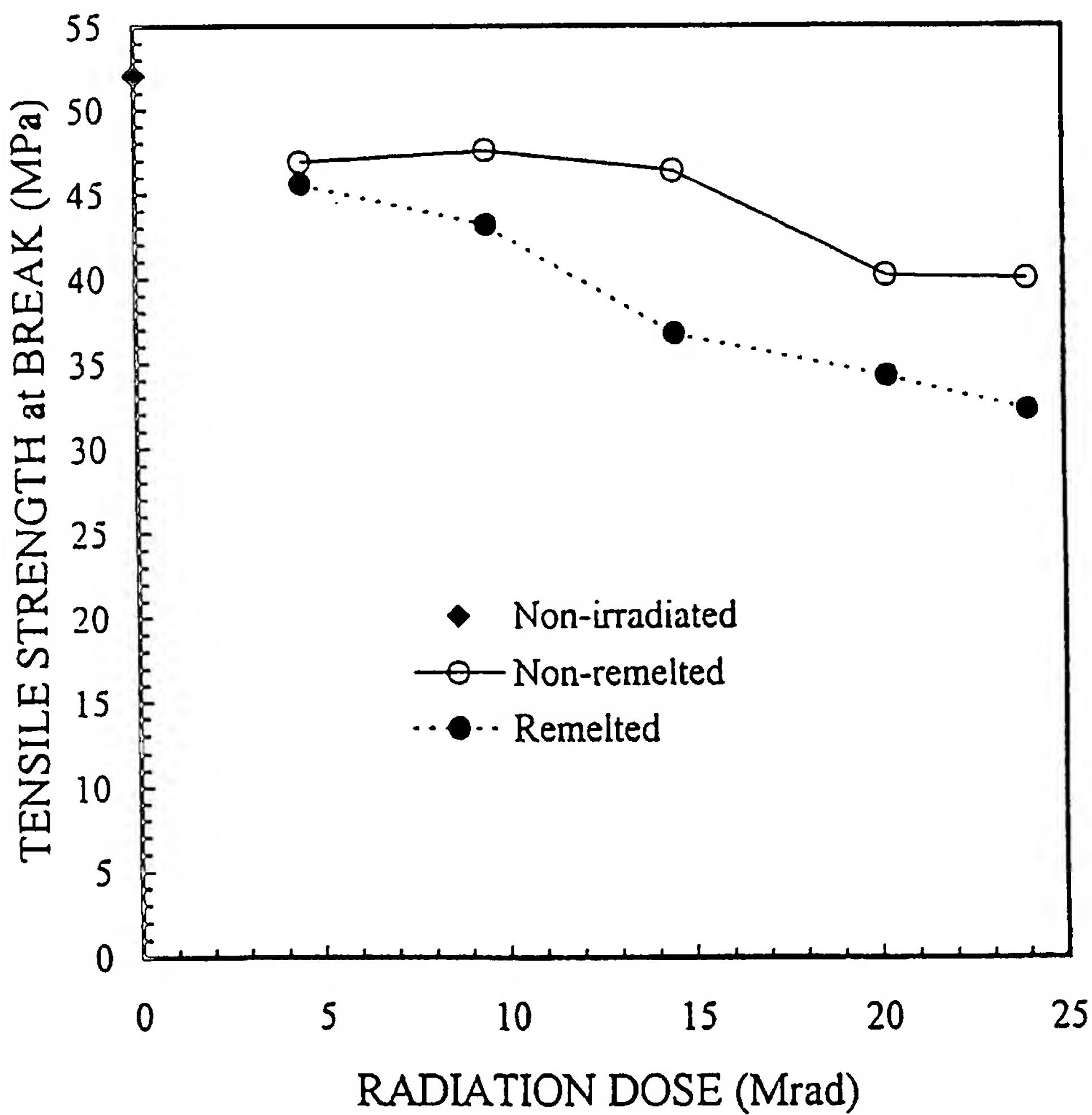


FIG. 26

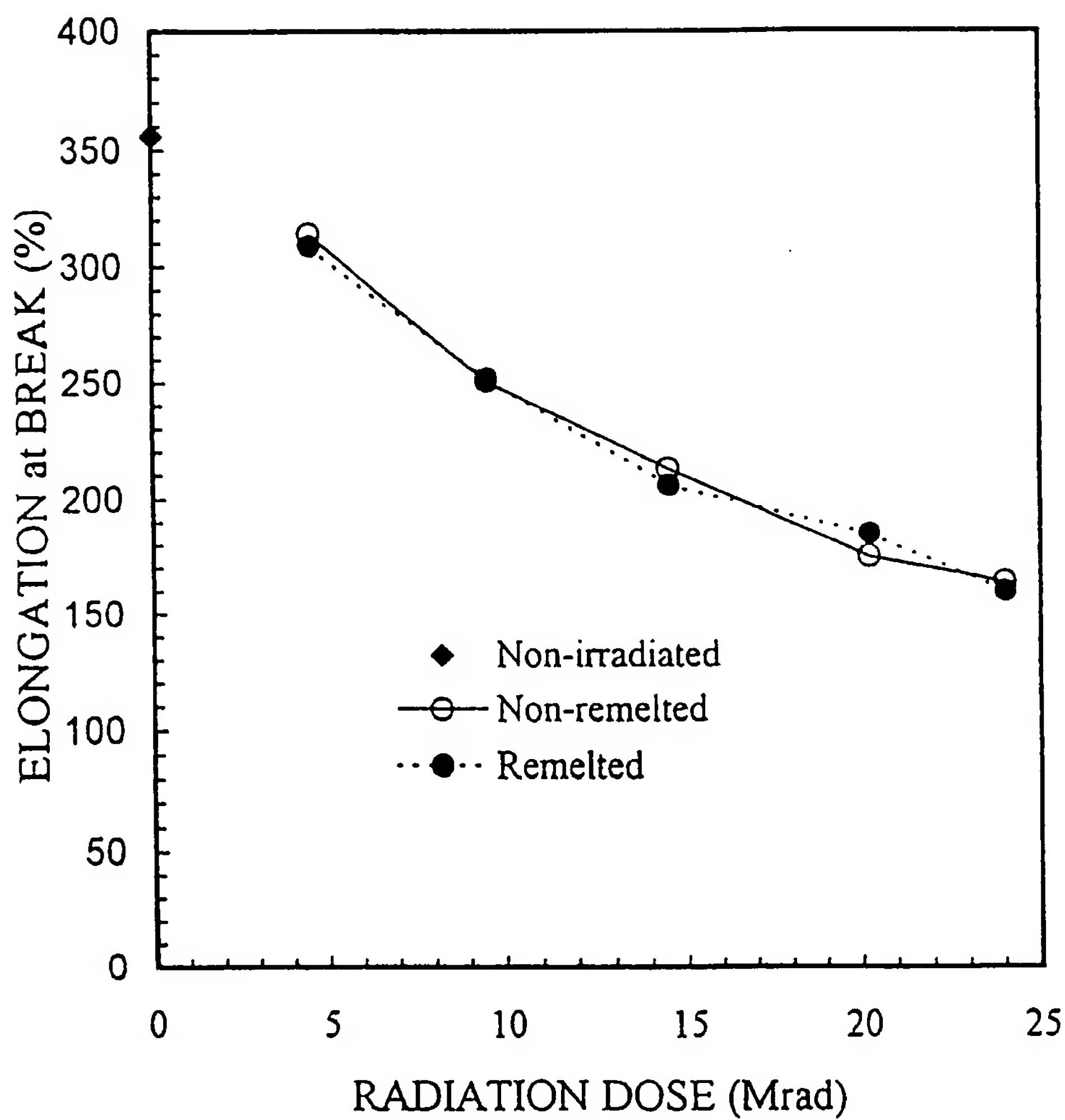


FIG. 27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/11947

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61F 2/00, 2/32, 2/34; C08J 3/28, 5/16; C08F 110/02, 110/06.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 522/153, 161, 163, 164; 523/113, 115; 525/937; 526/351, 352; 623/18, 19, 20, 21, 22, 23.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---	US 4,281,420 A (RAAB) 04 August 1981, Abstract, column 3, lines 19-40, column 5, lines 15-62, column 6, line 34, to column 7, line 11, Examples 2 and 6.	1, 5-7, 10, 13, 15, 16, 21, 23-25, 28-30
Y		----- 2-4, 8, 9, 11, 12, 14, 17-20, 22
A	US 4,055,862 A (FARLING) 01 November 1977, Abstract, column 4, lines 1-51.	1-30
X ---	US 5,439,949 A (LUCAS ET AL) 08 August 1995, column 3, line 41, to column 4, line 34, column 6, lines 1-11, Example 1.	1, 6, 8, 15, 17, 28, 30
Y		----- 2-5, 7, 9-14, 16, 18-27, 29

 Further documents are listed in the continuation of Box C.

See patent family annex.

• Special categories of cited documents:	*T*	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
31 OCTOBER 1997

Date of mailing of the international search report

28 NOV 1997

Name and mailing address of the ISA/US
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Washington, D.C. 20231
Facsimile No. (703) 305-3230Authorized officer
SUSAN BERMAN

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/11947

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	US 5,577,368 A (HAMILTON ET AL) 26 November 1996, column 3, lines 35-53, column 4, lines 8-16, column 4, line 63, to column 5, line 4, column 5, lines 39-64, Examples 1-4.	1-30
Y	US 5,210,130 A (HOWARD, JR.) 11 May 1993, column 2, line 49, to column 3, line 17, column 5, lines 30-34.	1-30
Y	US 4,582,656 A (HOFFMAN) 15 April 1986, column 1, line 59, to column 2, line 28, Example 1.	1-30
X ----	US 5,200,439 A (ASANUMA) 06 April 1993, column 3, line 27, to column 4, line 5, Examples 1-6.	1-4, 6, 8, 9, 12, 15, 17, 18, 23, 28, 30 -----
Y		5, 7, 10, 11, 13, 14, 16, 19, 24-27, 29 -----
X ---	US 2,948,666 A (LAWTON) 09 August 1960, column 2, line 55, to column 3, line 23, column 4, lines 47-66, Examples.	1, 6, 8, 13, 15, 17, 21, 23, 28, 30 -----
Y		2-5, 7, 9-12, 14, 16, 19, 20, 22, 24-27, 29

INTERNATIONAL SEARCH REPORT

International application No. PCT/US97/11947

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/11947

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

522/153, 161, 163, 164; 523/113, 115; 525/937; 526/351, 352; 623/18, 19, 20, 21, 22, 23.

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS: prosthetic or artificial joints, acetabular, hip, in vivo implants, bearing surfaces, moving contact, sliding, pivoting, rotating, UHMWPE, HIFAX 1900, GUR 4020, 4120, 4150, polymethylmethacrylate, nylon, polycarbonate, polyethylene, polypropylene, irradiation, photocrosslinking, crystallinity, gel content

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-25, drawn to a thermally treated crosslinked polymer, method of preparing the polymer and in vivo implant comprising the polymer.

Group II, claim(s) 26-30, drawn to a method for determining optimal radiation dose and thermal treatment for treating a polymer and to the product produced.

The inventions listed as Groups I-II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: (1) the steps for determining radiation dose and remelting or annealing conditions set forth in the claims of Group II are not required in the method set forth in the claims of Group I (2) the characteristics of the polymeric composition set forth in the claims of Group I are not mentioned in the claims of Group II.

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CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
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DK	Denmark	LR	Liberia	SG	Singapore		

TITLE

Process for Medical Implant of Cross-linked Ultrahigh Molecular Weight
Polyethylene Having Improved Balance of
Wear Properties and Oxidation Resistance

5

BACKGROUND OF INVENTIONField of Invention

This invention relates to a process for forming medical implants of cross-linked ultrahigh molecular weight polyethylene having an improved balance of wear properties and oxidation resistance.

10 Description of Related Art

It is known in the art that ultrahigh molecular weight polyethylene (UHMWPE) can be cross-linked by irradiation with high energy radiation, for example gamma radiation, in an inert atmosphere or vacuum. Exposure of UHMWPE to gamma irradiation induces a number of free-radical reactions in the polymer. One of these is cross-linking. This cross-linking creates a 3-dimensional network in the polymer which renders it more resistant to adhesive wear in multiple directions. The free radicals formed upon irradiation of UHMWPE can also participate in oxidation which reduces the molecular weight of the polymer via chain scission, leading to degradation of physical properties. 20 embrittlement and a significant increase in wear rate. The free radicals are very long-lived (greater than eight years), so that oxidation continues over a very long period of time resulting in as much as a 5-fold increase in the wear rate as a result of oxidation over a period of about 5 years. As such, the wear rate of traditionally irradiated materials is significantly greater than unirradiated materials.

25 Sun et al. U.S. Patent 5,414,049, which patent is hereby incorporated by reference, discloses a process for improving the oxidation resistance of medical implants which have been sterilized with radiation. In a preferred embodiment, a raw polymeric material is obtained by forming a virgin resin powder from which air and moisture have been removed prior to the forming process. The forming 30 process, e.g. ram extrusion or compression molding of the powder is also preferably carried out in an inert low oxygen atmosphere. A medical implant is formed from the raw material, e.g. an olefinic material such as UHMWPE, and is

sealed in an oxygen impermeable package in an oxygen reduced non-reactive atmosphere and radiation sterilized, followed by heating the sterilized packaged implant at a temperature of between 37°C and the melting point of the olefinic material. The heating step forms cross-links between remaining free radicals 5 formed during the radiation sterilization step, thus improving the oxidation resistance of the material. If the annealing temperature is too high, the thermal treatment can cause distortion of the UHMWPE implant, which is undesirable in orthopedic end-uses where the implants are generally machined or molded to close tolerances. If the temperature profile during annealing is adjusted to lower 10 temperatures to avoid distortion of UHMWPE implants, incomplete extinguishing of the free radicals generally occurs and the UHMWPE oxidizes upon exposure to air or moisture.

Hyun et al. published International Application WO 96/09330, which application is hereby incorporated by reference. discloses a process for forming 15 oriented UHMWPE materials for use in artificial joints by irradiating with low doses of high-energy radiation in an inert gas or vacuum to cross-link the material to a low degree, heating the irradiated material to a temperature at which compressive deformation is possible, preferably to a temperature near the melting point or higher, and performing compressive deformation followed by cooling and 20 solidifying the material. The oriented UHMWPE materials have improved wear resistance. Medical implants may be machined from the oriented materials or molded directly during the compressive deformation step. The anisotropic nature of the oriented materials may render them susceptible to deformation after machining into implants.

25 Salovey et al. published European Application EP 722973, which application is hereby incorporated by reference. discloses a method for enhancing the wear-resistance of polymers, including UHMWPE, by crosslinking them via irradiation in the melt or using peroxide or similar chemical agents.

The process of the present invention eliminates the problem of thermal 30 distortion of the implant by irradiating and thermally treating a consolidated UHMWPE material prior to forming an implant therefrom. By separating the irradiation cross-linking step from the sterilization step, the current invention

allows one to use lower levels of irradiation for cross-linking than would be effective for sterilization of UHMWPE. Additionally, the heat treatment step following irradiation may be performed at temperatures near or above the melting point, which would distort the shape of a machined or molded implant which has 5 been packaged for final sterilization. Heat treatment near or above the melting point results in improved molecular mobility, elimination of free radicals in the crystalline regions of the polymer which cannot occur at temperatures below the melt, and increased cross-linking and reduced oxidation in aged samples. When heat treatment is carried out at lower temperatures, incomplete quenching of free 10 radicals results in residual oxidation upon aging. By separating the irradiating and annealing steps, the process of the current invention also avoids the need to irradiate in the melt, which is difficult to achieve on a commercial scale. An additional object of the current invention is to prepare a medical implant of cross-linked UHMWPE having improved wear properties without the use of chemical 15 cross-linking agents. Medical implants formed from the cross-linked UHMWPE material of the current invention may be packaged in an air-permeable package and sterilized using non-irradiative methods such as gas plasma or ethylene oxide, eliminating the need to package the implants in an inert atmosphere. The cross-linked UHMWPE of the current invention can also be used in nonmedical 20 applications requiring high wear resistance.

SUMMARY OF THE INVENTION

The current invention pertains to a process for preparing cross-linked ultrahigh molecular weight polyethylene useful in medical implants. The process involves irradiating a preform of ultrahigh molecular weight polyethylene. 25 preferably with gamma radiation. Optionally, the preform may be annealed prior to irradiation in an inert atmosphere without the application of external pressure. The irradiated preform is then annealed in a substantially oxygen free atmosphere at a temperature at or above the onset of melting temperature, preferably near or above the peak DSC melting point, for a sufficient time to substantially recombine 30 (eliminate) all the free radicals and crosslink the ultrahigh molecular weight polyethylene. This annealing step may be done under isostatic or hydrostatic pressure. The annealed preform is cooled while maintaining the oxygen free

atmosphere and formed into a medical implant. The implant is sterilized using non-irradiative methods. Sterilization preferably is done by packaging the implant in an air permeable package and treating with gas plasma.

The invention further pertains to an improved cross-linked ultrahigh molecular weight polyethylene that can be made by the process of this invention. This cross-linked ultrahigh molecular weight polyethylene preferably has a swell ratio of less than about 5 and oxidation level of less than about 0.2 carbonyl area/mil sample thickness after aging under an oxygen pressure of about 5 atmospheres. It preferably has a percent elongation at break of at least 250, a single notch IZOD strength of at least 15 foot pounds per inch (ft lb/in) of notch, and a double notch IZOD strength of at least 35 ft lb/sq. in. The medical implant of this cross-linked ultrahigh molecular weight polyethylene exhibits an improved balance of wear properties and oxidation resistance. Wear properties are superior to those of conventional ultrahigh molecular weight polyethylene sterilized using gas plasma or gamma-irradiation. Oxidative resistance is significantly improved over conventional gamma-sterilized ultrahigh molecular weight polyethylene and is comparable to unirradiated, gas plasma sterilized ultrahigh molecular weight polyethylene.

DETAILED DESCRIPTION

For the purposes of this invention ultrahigh molecular weight polyethylene is defined as a polyethylene having an estimated weight average molecular weight in excess of about 400,000, usually 1,000,000 to 10,000,000 as defined by a melt index (ASTM D-1238) of essentially zero and a reduced specific viscosity greater than 8, preferably 25-30.

An UHMWPE preform is used as the starting material in the current process. The term preform is used herein to refer to a shaped article which has been consolidated, such as by ram extrusion or compression molding of UHMWPE resin particles into rods, sheets, blocks, slabs or the like. Such preforms may be obtained or machined from commercially available UHMWPE, for example GUR 4150 HP ram extruded UHMWPE rods from PolyHi Solidur (Fort Wayne, Indiana). The starting preform may also be pressure recrystallized as described in Howard U.S. Patent 5,478,906, which patent is hereby incorporated

by reference. The UHMWPE preform material does not contain stabilizers, antioxidants, or other chemical additives which may have potential adverse effects in medical applications.

The process of the current invention includes the steps of irradiating a
5 UHMWPE preform to form free radicals and cross-link the UHMWPE, annealing the irradiated UHMWPE preform at elevated temperature in a substantially oxygen free atmosphere to eliminate any free radicals remaining from the irradiation step, thus further cross-linking and increasing the oxidation resistance of the irradiated UHMWPE, and forming a medical implant from the annealed
10 cross-linked preform. Gamma radiation is preferably used in the irradiation step, however electron beam or x-ray radiation may also be used. Ultrahigh molecular weight polyethylene prepared according to the process of the current invention has an improved balance of wear properties and oxidation resistance. The increased cross-linking results in reduced swell ratios, generally less than about 5, and
15 improved wear performance with comparable oxidation resistance relative to unirradiated UHMWPE.

The preform is preferably irradiated in the solid state with gamma radiation at a dose of about 0.5-10 Mrad using methods known in the art. Preferably, the preform is irradiated at a dose of about 1.5 - 6 Mrad. Radiation
20 doses of less than about 0.5 Mrad generally provide insufficient cross-linking to provide the desired increase in wear properties in the final implant. While doses of greater than 10 Mrad may be used, generally the additional improvement in wear properties that is achieved by the higher dose is offset by increasing brittleness of the UHMWPE due to higher levels of cross-linking. Ultrahigh
25 molecular weight polyethylene prepared using the process of the current invention generally has a percent elongation at break of at least about 250, single notch Izod strength of at least about 15 ft lb/in of notch, preferably at least about 17 ft lb/in of notch, and double notch Izod strength of at least about 35 ft lb/sq in. UHMWPE which has been pre-annealed or annealed at temperatures greater than about 280°C
30 generally have a percent elongation at break of at least about 400, preferably at least about 500. The irradiation step is generally performed at room temperature, however higher temperatures may be used.

The preform is optionally contained in an inert atmosphere or vacuum, such as in an oxygen impermeable package during the irradiation step. Inert gases such as nitrogen, argon, and helium may be used. If a vacuum is used, the packaged material may be subjected to one or more cycles of flushing with an inert gas and applying a vacuum to eliminate oxygen from the package. Examples of packaging materials include metal foil pouches such as aluminum or MYLAR® polyester coated packaging foil which is available commercially for heat-sealed vacuum packaging. Polymeric packaging materials such as polyethylene terephthalate and poly(ethylene vinyl alcohol), both of which are commercially available may also be used. Irradiating the preform in an inert atmosphere reduces the effect of oxidation and accompanying chain scission reactions which can occur during gamma-irradiation. Oxidation that is caused by oxygen which is present in the atmosphere during irradiation is generally limited to the surface of the preform. Since the process of the current invention radiation cross-links the UHMWPE prior to forming the implant, low levels of surface oxidation can be tolerated as the oxidized surface can be removed during subsequent machining of the implant from the preform.

After the UHMWPE preform has been gamma irradiated, it is heat treated by holding at elevated temperature in a substantially oxygen-free atmosphere. typically created by introducing inert gas or employing a vacuum, for a time that is sufficient to recombine substantially all of the free-radicals which remain in the material from the irradiation cross-linking step, thus further cross-linking the material and stabilizing it to oxidation. Thermal distortion of the preform material during heat treatment may occur without affecting the final implant since the implant is formed from the preform after heat treatment. This allows higher temperatures to be used than would be possible in processes where the finished implants are heat treated. The hold time required for reaction of the free radicals decreases with increasing temperature. Thus, a wide range of temperatures, including temperatures above the melting point of the UHMWPE, is acceptable in the heat treatment step of the current invention.

The irradiated preform preferably is heated at a temperature at or above the onset of melting temperature of the irradiated heat-treated preform material, and

preferably at a temperature near or above the peak melting temperature of the irradiated heat-treated polymer for a time of 2-120 hours, preferably 5-60 hours, more preferably 12-60 hours. The onset of melting temperature is defined herein as the temperature at the intersection of the baseline and steepest negative slope of the DSC melting endotherm. The baseline intersects the initial portion of the melting endotherm and is tangent to the final portion of the curve. The peak melting temperature is defined herein as the location of the peak of the melting endotherm. The onset of melting temperature for irradiated, heat-treated UHMWPE is generally about 120°C and the peak melting temperature is generally between 135°C and 140°C. An especially preferred embodiment of the current invention is irradiation with a dose of 1.5 - 6 Mrads followed by heat treatment at 150-170°C for a period of 6-60 hours, more preferably 12-60 hours. The temperature and hold time that is sufficient to react substantially all of the free-radicals may be determined by measuring the oxidation of the samples using the method described below. Preferably, the temperature and hold time are chosen such that oxidation levels of less than about 0.2 carbonyl area/mil sample thickness, preferably less than about 0.1 carbonyl area/mil sample thickness, after aging as measured by this method are obtained. Heat treatment at or above the onset of melting temperature results in improved molecular mobility and elimination of free radicals in the crystalline regions of the polymer and increased cross-linking and reduced oxidation in aged samples. When heat treatment is carried out at lower temperatures, elimination of free radicals is less complete resulting in higher levels of residual oxidation upon aging.

Standard UHMWPE may be irradiated and pressure recrystallized to convert the UHMWPE into an extended chain conformation by conducting the heat treatment step using the temperatures and pressures disclosed for pressure recrystallization in U.S. 5,478,906. In pressure recrystallizing UHMWPE, the polymer is placed in a pressure vessel in water and enough pressure to withstand the pressure the water will develop at the operating temperatures. The temperature of the vessel is raised to melt the polyethylene which generally melts at 135-150°C at one atmosphere, and about 200°C at 50,000 psi. The time required to melt the polymer depends on the size of the UHMWPE preform used.

Because UHMWPE is a poor heat conductor and has a very high heat of crystallization, it can take 1-2 hours to heat a 3 in. diameter rod to 200°C with the vessel at 220°C. Once the polymer is hot and molten, the pressure is applied. Preferred pressures are about 33 kpsi (230 MPa) to 70 kpsi (480 MPa). Further improvement in properties may be achieved by annealing the UHMWPE in an inert atmosphere at temperatures above the melting point prior to pressure recrystallization. Pressures of greater than 45 kpsi (310 MPa) are preferred for pressure recrystallization of material which is pre-annealed prior to pressure recrystallization. The cooling time normally is about 6 hours from 250°C to 75°C, but forced cooling of the vessel can reduce this to 1-2 hours with no adverse effects on the product.

Preferably, the UHMWPE material prepared according to the process of the current invention is an isotropic material, with no significant molecular or crystalline orientation. In order to prevent inducing residual stress in the polymer, thermal treatment after irradiation is preferably performed in such a manner that no non-uniform forces which could lead to deformation of the material during heat treatment will occur. During heat treatment the preform can be subjected to uniform pressure, such as isostatic or hydrostatic pressure, or alternatively, the preform can be heated in the absence of any externally applied pressure, so as to not deform the UHMWPE. It is undesirable to deform the preform by application of compressive or other forces as this results in an oriented material which may deform due to internal stresses after machining of the implant.

After a predetermined time, the cross-linked preform is cooled while still in an inert atmosphere or vacuum. The cross-linked preform is cooled to a temperature less than about 100°C, preferably less than about 50°C, more preferably to room temperature, prior to exposing the preform to air. If the preform was packaged during the heat treatment step, after cooling it is removed from the packaging and formed into an implant using methods known in the art such as machining. The cross-linked UHMWPE is especially useful as a bearing surface, for example in prosthetic hip joint cups and as other prosthetic shapes for replacement of other joints of the human body, including knees, shoulders, fingers, spine, and elbows. The finished implant is then packaged and sterilized

using non-radical-forming methods. Because the implant is oxidatively stabilized, it is not necessary to package the finished implant in an inert atmosphere. For example, the implant can be packaged in air-permeable packaging and sterilized using gas plasma or ethylene oxide methods which are known in the art. For 5 example a PLAZLYTE® gas plasma sterilization unit, manufactured by Abtox (Mundelein, Illinois), may be used.

In an alternate embodiment of the current invention, the UHMWPE preform is pre-annealed prior to the irradiation step. In the pre-annealing step, the preform is subjected to a temperature of 280°C - 355°C, preferably 320°C-10 355°C, for at least 0.5 hour, preferably at least 3 hours, in an inert atmosphere, without the application of external pressure. It is generally desirable to heat the polymer as close as possible to, without reaching, its decomposition temperature. The pre-annealed preform is then cooled non-precipitously to a temperature of about 130°C or below, the rate of cooling being such that temperature gradients 15 producing internal stresses in the article are substantially avoided. Rapid cooling, such as by immersion in cold water, should be avoided as it causes internal voids to form. It is generally convenient to allow the polymer to cool wrapped in insulation. The pre-annealed preform has improved elongation, impact resistance, and crystallinity over the starting UHMWPE. The cooled pre-annealed preform is 20 then irradiated and annealed as described above.

TEST METHODS

Unless noted otherwise, test specimens were prepared from the interior of the preform rods.

Type IV tensile specimens conforming to ASTM D-638 were machined 25 from the UHMWPE sample materials. The test specimens were mounted in a Lloyd LR10K mechanical test frame and tested for the tensile yield stress (TYS), ultimate tensile stress (UTS) and percent elongation according to ASTM D-638. Type IV specimens were used to measure UTS, TYS, and percent elongation for Examples 1-27, and Comparative Examples A-C.

30 Type I tensile specimens were machined from the UHMWPE samples and mounted in the test frame. Tensile modulus was measured on these samples according to ASTM D-638. Type I tensile specimens were also used to measure

TYS, UTS and percent elongation for Examples 28-37 and Comparative Example D.

All tensile properties represent the average of 5 test specimens.

Thermal analysis was performed on disks approximately 3 mm thick and 5 1.5 mm in diameter which were cut from the UHMWPE sample rod. The disk was placed in a differential scanning calorimetry (DSC) sample pan and weighed. The lid was placed on the pan and crimped in place. The pan was placed in a DuPont Model 2000 thermal analyzer and allowed to equilibrate at a temperature of 50°C. It was then heated at a rate of 20 degrees C/minute. The peak melting 10 point was taken as the location of the peak of the melting endotherm. The onset of melting temperature was determined from the DSC curve as the intersection of the baseline and the steepest negative slope of the melting endotherm. The baseline intersects the initial portion of the melting endotherm and is tangent to the final portion of the curve. The heat of fusion (Hf) was calculated as the area of 15 the melting endotherm.

The percent crystallinity was determined by dividing the measured heat of fusion by the theoretical heat of fusion of crystalline UHMWPE, 290 J/g.

Density measurements were performed on 1.5 mm thick disks of UHMWPE cut from the UHMWPE sample rods. The disks were soaked in a 20 65/35 solution by weight of 2-propanol, histological grade, and water. The sample was placed into a calibrated density gradient column. The density was determined from the equilibrium position of the sample in the column and is reported as g/cc.

Resistance to deformation (creep) was measured in accordance with 25 ASTM D-621 with the following modifications: samples machined into cylinders or cubes without the use of lubricating liquids; samples measured 0.5 in. x 0.5 in. x 0.5 in.

Impact resistance was measured using the notched Izod test given in 30 ASTM D-256 with the following modifications: samples machined into shape without the use of lubricating liquid; type A or notched IZOD; specimen size was 0.5 in. x 2.5 in.: 0.4 in. from bottom of vertex to opposite side: 1.25 in. impacted end (from end of bar to vertex of notch); the notch should be the specified angle of

22.5 degrees. Impact strength was also measured using double notched Izod specimens and the test method described in ASTM F-648 Annex A1.

Oxidative aging was performed on specimens which were wrapped in porous breather fabric to prevent close packing of the specimens and allow free 5 gas access to all surfaces. The specimens were then loaded into a 4 in. x 8 in. cylindrical pressure bomb and sealed. The bomb was pressurized to 5 atmospheres (73.5 psi) with oxygen and heated with cylindrical band heaters to 70°C and held for 14 days. Aged wear test results were obtained by aging the hip 10 cups using this procedure prior to wear testing. Similarly, aged Izod specimens for double notch impact strength measurements were prepared according to ASTM F-648 Annex A1 followed by oxidative aging prior to strength measurements.

Specimens for oxidation measurements were cut from the interior of the cooled preform rods after gamma-irradiation and annealing. The samples were 45 15 degree wedge cuts from 0.5 inch thick by 2.5 inch diameter disks. Oxidation measurements were made on 250 micron thick sections prepared by cutting the wedge-shaped specimens through their thickness using a band saw. A 250 micron thick slice was microtomed off the freshly exposed surface and analyzed using FTIR. Aged oxidation results were obtained from wedge cuts that were aged 20 according to the oxidative aging procedure described above prior to preparing the 250 micron thick section. The sample was mounted in a Digilab FTIR fitted with a microscope with a motorized stage. The FTIR aperture was focused through the microscope to allow measurement of the infrared absorbance in a small (25 micron x 200 micron) section of the sample. The microscope stage was moved by 25 a stepper motor in increments of 50 microns to measure the carbonyl absorbance at a number of locations from the surface down to a depth of 4 mm. Oxidation was quantified based on the absorbance of the carbonyl peaks at 1670 - 1730 wavenumbers as compared to a reference peak corresponding to methylene stretching along the polymer backbone at 4250 wavenumber using the method of 30 Nagy & Li. A Fourier Transform Infrared Technique For The Evaluation of Polyethylene Bearing Materials, Transactions, 16th Annual Meeting, The Society for Biomaterials, 3:109, 1990. An average oxidation level was calculated by

integrating the carbonyl concentration versus depth curve to a depth of 2.05 mm.

Oxidation is reported as carbonyl area/mil sample thickness.

Swell ratios were measured per ASTM D 2765 method C. The test specimens were .32 inch cubes. All swell ratios represent the average of 4 test 5 specimens.

Gas plasma sterilization was performed by (a) placing the component in a breathable pouch and heat sealing, (b) placing the packaged components in the chamber of a PLAZLYTE® Sterilization System (Abtox, Inc., Mundelein, Illinois) and evacuating (c) filling the chamber with peracetic acid vapor and 10 holding for a predetermined time. (d) evacuating the chamber, (e) filling the chamber with a filtered secondary plasma and holding for a predetermined time. (f) evacuating the chamber, (g) repeating steps (c)-(f), (h) filling the chamber with atmospheric air, (i) evacuating the chamber, and (j) repeating steps (h) and (i) to complete the cycle.

15 Wear rates were obtained by mounting test hip cups having a 28 mm spherical hole in the cup in a hip simulating wear tester which included 28 mm diameter femoral heads. The test cups were machined from the interior of the preform rods and were pre-soaked for 30 days in bovine calf serum solution containing 20 mM EDTA and 0.2 wt% sodium azide. The cups were sterilized by 20 gas plasma prior to wear testing. The wear tester simulated the human gait using the Paul hip curve at a 1900 N peak load and a frequency of 1.1 Hz. The load is applied in the vertical direction. The test cup in the hip simulator is immersed in bovine calf serum and angled at 23 degrees from the horizontal. Every 500,000 cycles, the cups are washed, dried and weighed. Each test was run between 2.5 25 and 5 million cycles. Soak controls cups were used to correct for fluid absorption. The wear rate is the soak corrected change in cup weight per million cycles.

EXAMPLES

In each of Examples 1-3, 28-37, and Comparative Examples A-D, the UHMWPE preform comprised GUR 4150 HP ram-extruded UHMWPE (PolyHi 30 Solidur, Fort Wayne, Indiana) in the form of 3.5 in. (8.9 cm) diameter rods approximately 30 in. (76.2 cm) in length. This polymer has a molecular weight of

approximately 6 million, a peak melting point of about 135°C, and a percentage crystallinity of about 45-55%.

Examples 1-3

5 Rods of UHMWPE as described above were placed in separate pouches of heat sealable packaging foil having a MYLAR® polyester coating, SP Class E style 1.40 sleevestock (Shield Pack, Inc., West Monroe, La), flushed with nitrogen and then evacuated. This procedure was repeated and the pouches were then sealed under vacuum. The rod of Example 1 was irradiated with a dose of 1 Mrad
10 of gamma irradiation from a Cobalt-60 source. Gamma irradiation was performed by Isomedix (Morton Grove, Illinois). The rods of Examples 2 and 3 were irradiated with doses of 2.5 Mrads and 5 Mrads, respectively. After irradiation, the packaged rods were placed individually in an oven at a temperature of 325°C and held at that temperature for 4.5 hours. At the end of 4.5 hours, the rods were
15 cooled in the oven at about 20°C/hr to ambient temperature in their packages. The cooled rods were then removed from their packages and mechanical and physical properties and oxidation were measured as described above. The results and process conditions are shown in Table I. These examples show excellent oxidation resistance under both aged and unaged conditions compared to
20 Comparative Examples A, B, and C. The effect is greatest for Example 3 (vs. Comparative Example C) which was irradiated at the higher dose of 5 Mrads. Aged and unaged oxidation resistance for Examples 1-3 is comparable to unirradiated Example D. This improved performance is due to the substantially complete quenching of the free radicals by annealing at 325°C. These examples
25 also show an unexpected benefit of a large increase, approximately 2x, in the % elongation to break, attributed to the temperature of the annealing. Elongation generally increases significantly for samples which are annealed or pre-annealed at temperatures of greater than about 280°C.

30 Comparative Examples A-C

UHMWPE rods for comparative Examples A and C were packaged under vacuum as described in Examples 1-3, and irradiated at doses of 1 Mrad and 5.0

Mrad, respectively. The rod of Comparative Example B was irradiated with 2.5 Mrad in air without packaging. The rods were not heat-treated after irradiation. Mechanical and physical properties and oxidation were measured as described above. The results and process conditions are shown in Table I. Test specimens 5 were taken from the interior of the rod, thus substantially eliminating any effects of oxidation in comparative Example B which was irradiated in air. For Example B, an unaged wear rate of 15 mg/million cycles and an aged wear rate of 88 mg/million cycles were measured after 5 million cycles. These examples show oxidative degradation in the accelerated aged state, demonstrating the reaction of 10 unquenched free radicals with oxygen. Example B also shows the effect of this oxidation on impact strength and wear. Impact strength is reduced by a factor of 10 after aging. Although the unaged wear rate for Example B is improved compared to Comparative Example D, the wear rate is increased by nearly 6X after aging, significantly higher than the wear rate for Comparative Example D.

15

Comparative Example D

The UHMWPE rods for this example were not irradiated, heat treated or pressurized. They were gas plasma sterilized by a PLAZLYTE® Sterilization System (Abtox Inc., Mundelein, Illinois). The mechanical and physical properties 20 are similar to commercially available UHMWPE rods and are shown in Table V. An unaged wear rate of 30 mg/million cycles and an aged wear rate of 33 mg/million cycles were obtained after 5 million cycles.

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Hoechst GUR 415 UHMWPE in the form of 3 in. (7.6 cm) diameter rods obtained from PolyHi Solidur were cut to about 15 in. (38.1 cm) length and sealed in polyethylene lined aluminum foil bags under a nitrogen atmosphere.

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The rods were irradiated with Co-60 gamma rays and aged for one month in the sealed bags to permit the free radicals to react. Irradiation doses of 0.5, 1, 2, and 5 Mrad were used. The bars were then removed from the bags and immediately placed in a pressure vessel, as described in Simmons et al. U.S. Patent 5,236,669, which patent is hereby incorporated by reference. Pressure

recrystallization was conducted by sealing the vessel and pressurizing with water to about 5000 psi. The vessel was then heated over a period of 1.5 hours to 250°C. After 2 hours, the pressure was raised to 50,000 psi and maintained there for the rest of the pressure treatment. After 1 to 2 hours at 250°C, the vessel was 5 allowed to cool to 75°C at which point the pressure was released and the product recovered. Additional rods were also pressure recrystallized using the above procedure at 39.000 and 34.000 psi. The results are shown in Table II.

Examples 16-21

10 In these examples, the 3 in. diameter GUR 415 UHMWPE rods were pre-annealed at 325°C for 4.5 hours in nitrogen, cooled in nitrogen at approximately 20°C/hr, and then sealed in aluminum foil/polyethylene bags under nitrogen. The bars were then irradiated with gamma rays. After aging one month, the polymers were pressure recrystallized as described above. Process conditions and results 15 are given in Table III. The polymer was converted to extended chain form only at higher pressure. The samples treated with 50.000 psi during pressure recrystallization had higher melting points, higher heats of fusion, higher tensile moduli, higher maximum strengths, higher tensile strength at yield, higher Izod impact strength, and improved creep resistance.

20 The pre-annealed samples of Examples 16-21 have higher elongations than the corresponding samples of Examples 4, 5, 7, 8, 10 and 11 which were not pre-annealed.

Examples 22-23

25 In these examples, 3 in. diameter GUR 415 UHMWPE rods were gamma irradiated at 2.5 Mrad and 5.0 Mrad in nitrogen and pressure recrystallized at 39,500 psi using the process described in Examples 4-15. Irradiation conditions and results are given in Table IV.

30 Examples 24-25

In these examples, 3 in. diameter GUR 415 UHMWPE rods were gamma irradiated at 2.5 Mrad and 5 Mrad, and then subjected to pressure recrystallization

at 33.500 psi using the process described in Examples 4-15. Irradiation conditions and results are given in Table IV.

Examples 22-23 and 24-25 show excellent oxidation resistance in both the aged and unaged states as did Examples 1-3, also due to substantially complete 5 quenching of free radicals during the pressure recrystallization step. The samples also show increased crystallinity, which in turn shows that it is possible to change the crystal structure of the polymer even in the presence of crosslinks.

Examples 26-27

10 In these examples, 3 in. diameter GUR 415 UHMWPE rods were pre-annealed in nitrogen at 325°C for 4.5 hours prior to gamma irradiation, cooled at approximately 20°C/hr. followed by gamma irradiation under nitrogen at 2.5 Mrad and 5 Mrad. and then subjected to pressure recrystallization at 39.500 psi using the process described in Examples 4-15. Irradiation conditions and results are 15 given in Table IV. These examples show that by combining a pre-annealing step (325°C) with pressure recrystallization after irradiation, oxidation resistance is maintained. the elongation is increased and the crystallinity increased compared to conventional UHMWPE (Comparative Example D).

20 Example 28-30

UHMWPE rods 28 - 30 were packaged and processed as described in Example 2 (2.5 Mrad) except that the rods were heated at 155°C for 6, 24, and 48 hours respectively, removed from the oven and cooled. The process conditions, mechanical and physical properties are shown in Table V. These examples show 25 that annealing at 155°C creates a material with excellent oxidation resistance. Irradiated samples 28-30 exhibited a reduction in double notched Izod compared to the unirradiated Comparative Example D. It also shows that the crosslinking produced by the 2.5 Mrad radiation dose yields a swell ratio of 3.9 as compared to 24.1 for Example D. An unaged wear rate of 14 mg/million cycles was measured 30 after 5 million cycles for hip cups prepared from the cross-linked polymer of Example 30.

Examples 31-33

UHMWPE rods 31, 32 and 33 were packaged and processed as described in Example 3 (5 Mrad) except that the rods were heated to 155°C for 6, 24 and 48 hours respectively, removed from the oven, and cooled. The process conditions, 5 mechanical and physical properties are shown in Table V. These examples show that UHMWPE exposed to 5 Mrads of gamma irradiation then annealed at 155°C also gives excellent oxidation resistance. It also shows that the radiation dose reduces the impact strength and the elongation. A comparison of these swell ratios, 2.6, with Examples 28-30 and D. show that crosslinking is increased with 10 radiation dose. An unaged wear rate of 0.8 mg/million cycle and an aged wear rate of 0.6 mg/million cycles were measured for Example 32 after 2.5 million cycles. The wear rate of Example 32 is greatly reduced compared to Examples 30, B and D. By performing both the irradiation and annealing steps, the wear and 15 oxidation resistance of this material is greatly improved over material that is irradiated but not annealed. Oxidation resistance is comparable to unirradiated polymer (Comparative Example D) and wear performance is significantly improved.

Example 34-36

20 UHMWPE rods 34, 35 and 36 were packaged and processed as described in Example 3 (5 Mrad) except that the rods were heated to 200°C for 6, 24 and 48 hours respectively, removed from the oven and cooled. The process conditions, mechanical and physical properties are shown in Table V. These examples show that annealing at 200°C is also effective for producing an oxidation resistant 25 material.

Example 37

This rod was packaged and processed as described in Example 3 (5 Mrad) except the rod was heated to 120°C for 48 hours, removed from the oven, and 30 cooled. An unaged wear rate of 5 mg/million cycles was measured after 5 million cycles. Results are shown in Table V. This example shows the improved wear resistance of a material crosslinked at 5 Mrads and annealed at 120°C for 48 hours

as compared to Examples 30 (2.5 Mrad, 155°C/48 hrs), C (5 Mrad, unannealed), and D (unirradiated).

TABLE I

	Example	1	2	3	A	B	C	D
5	Gamma dose (Mrad)	1	2.5	5	1	2.5	5	0
	Hold Temp/Time (deg C/hr)	325/4.5	325/4.5	325/4.5	none	none	none	none

Mechanical PropertiesType I Samples

10	Modulus (kpsi)	147.8	148.5	144.3		143.1		137.0
	Secant Modulus (kpsi)				122.3			

Type IV Samples

15	TYS	3.544	3.454	3.429	3.553	3.507	3.669	3.396 (Type I)
	UTS	5.603	5.481	5.644	5.324	5.47	5.511	5.152 (Type I)
	% Elongation	805	700	613	310	340	267	343 (Type I)
Impact Strength - Double Notched Izod (Ft-lb/sq in)								
	(unaged)					48.1		48.1
	(aged)					4.8		

20	<u>Physical Properties</u>							
	Density (g/cc)	0.9461	0.9442	0.9409	0.9356	0.9378	0.9379	.9344
	Hf (J/g)	170.9	184.2	161.6	145	163.3	165.8	
	% Crystallinity	58	63	55	50	56	57	51
25	Peak Tm (°C)	138.1	137.1	135.6	139.4	138.7	137.4	136.7
	Onset of melting T (°C)	126.0	125.8	123.0		127.2		130.8
	Oxidation(unaged)	0.067	0.048	0.068	0.154	0.172	0.398	054
	oxidation(aged)	0.14	0.078	0.117	0.527	1.107	2.78	.075
	Swell Ratio							24.1
30	<u>Wear Rate (mg/million cycles)</u>							
	(unaged)					15		30
	(aged)					88		33

TABLE II

Example	4	5	6	7	8	9	10	11	12	13	14	15
Gamma	0.5	0.5	0.5	1	1	1	2	2	2	5	5	5
Dose (Mrad)												
Pressure (kpsi)	50	39	34	50	39	34	50	39	34	50	39	34
Tensile												
Strength, psi												
Yield	3877	3668	3504	3804	3543	3470	3597	3524	3446	3628	3553	3394
Max	5871	6400	5936	6662	6463	5514	6551	5517	5047	5766	5205	5155
Break	5629	6397	4791	6570	5759	4995	6054	4462	5023	4877	5204	4220
Modulus (kpsi)	288.4	272.8	229.3	248.3	239.0	227.8	309.1	250.3	292.4	237.7	234.1	188.1
Elongation, %												
Yield	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Break	290	309	232	296	324	311	272.7	289.5	286.3	243	247	254
IZOD	19.6	20.1	19.8	19.7	19.6	19.1	19.8	19.8	18.7	19.4	17.4	17.9
ft lb/in of notch												
Deformation (%)	1.0	1.5	1.6	1.6	1.7	1.9	1.7	1.7	1.9	1.8	1.9	1.8
24 hrs., 23 deg. C.												
1000 psi.												
DSC												
Peak mp, deg C	147.6	144.8	138.3	147.6	147.3	137.2	150.4	150.4	145.5	146.0	145.7	147.7
Hf (J/g)	185.7	170.4	133.7	185.7	173.6	53.7	171.3	171.3	170.4	178.5	183.9	187.2
Peak mp, deg C *	S	S	145	S	S	143.9	S	S		S	S	
Hf (J/g)				58.4			125.2					

(*S stands for shoulder on low temperature side of DSC curve)

TABLE III

**Physical Properties of Pre-Annealed (325°C) UHMWPE,
Gamma Irradiated and Pressure Recrystallized**

5

Example	16	17	18	19	20	21
Dose (Mrad)	0.5	0.5	1	1	2	2
Pressure (kpsi)	50	39	50	39	50	39
Tensile Strength, psi						
Yield	4277	3773	4066	3543	4051	3594
Max	5289	4696	5145	4332	5142	4119
Break	4532	4695	4582	4331	4604	4117
Modulus (kpsi)	335.2	276.0	296.9	219.0	293.6	266.5
Elongation, %						
Yield	5	7.5	5	7.5		7.5
Break	>432	>500	>450	417	>400	388
IZOD (ft lb/in of notch)	24.0	20.5	24.2	21.6	23.6	21.9
Deformation (%) 24 hrs, 23 deg C, 1000 psi	0.7	2.8	0.8	1.8	1.2	2.3
DSC						
mp, deg C	148.8	140.7	148.9	140.8	148.6	140.8
Hf (J/g)	217	175	207	185.9	202.8	177.9

TABLE IV

Example	22	23	24	25	26	27
5 Gamma dose (Mrad)	2.5	5	2.5	5	2.5	5
10 Pre-annealing						
Heat/hold time (deg C/hrs)	none	none	none	none	325/4.5	325/4.5
Pressure (psi)	39.500	39.500	33.500	33.500	39.500	39.500

MECHANICAL PROPERTIES

15	<u>Type I Samples</u>					
	modulus (kpsi)	172.6	171.5	153.7	151.2	144.3
	Secant modulus (kpsi)	157	146.9	136.8	136.7	178.9
20						162.1
	<u>Type IV Samples</u>					
	TYS (kpsi)	3.565	3.591	3.423	3.508	3.926
	UTS (kpsi)	5.855	5.862	5.439	5.475	5.696
25	% Elongation	287	258	292	256	525
						568

PHYSICAL PROPERTIES

Density (g/cc)	0.9393	0.9396	0.9368	0.9381	0.9475	0.9461
Hf (J/g)	188.7	158.1	150.8	174.4	177.4	176.7
% Crystallinity	65.069	54.517	52	60.138	61.172	60.931
30 Tm (deg C)	143.5	143.8	143.1	143.5	134.7	136.3
oxidation(unaged)	0.055	0.082	0.092	0.074	0.082	0.065
oxidation(aged)	0.08	0.082	0.08	0.096	0.133	0.16

TABLE V

Example	28	29	30	31	32	33	34	35	36	37
Gamma dose (Mrad)	2.5	2.5	2.5	5	5	5	5	5	5	5
Heat/hold time (°C/hrs)	155/6	155/24	155/48	155/6	155/24	155/48	200/6	200/24	200/48	120/48

MECHANICAL PROPERTIES**Type I Tensile Samples**

Modulus (kpsi)	115.7	114.3	124.9	111.9	116.2	110.8	112.4	118.4	108.7
Secant mod. (kpsi)	106.5	104.6	114.3	99.3	104.9	101.8	100.6	109.6	98.5
TYS (kpsi)	3.080	3.100	3.056	3.068	3.147	3.113	3.075	3.115	3.094
UTS (kpsi)	5.130	5.436	5.024	5.037	5.238	5.267	4.698	5.053	5.000
% Elongation	331	326	321	272	273	283	265	263	278

Impact Strength, Double Notch (ft

lb/in ²									
(unaged)	44.0	44.7	44.0	36.2	35.1	37.3	37.3	38.3	36.9
(aged)	44.0	44.6	42.7	36.0	35.7	37.8	37.0	36.8	37.1
Deformation (%) (24 hrs, 23 °C, 1 kpsi)	1.5	1.1	1.4	1.2	1.6	1.0	1.0	1.2	1.2

PHYSICAL PROPERTIES

Density (g/cc)	0.9292	.9289	.9298	.9295	.9299	.9292	.9292	.9295	.9285
Hf (J/g)	135.6	146.3	132.5	141.2	128.5	147.4	131.4	142.9	145.8
% Crystallinity	47	50	45	49	44	51	45	49	50
Peak Tm (°C)	134.7	134.4	135.1	137.8	136.6	134.9	134.8	137.3	135.8
Onset of melting T _g (°C)	121.8	123.6	122.7	121.3	120.9	120.1	119.9	121.8	120.5
oxidation									
(unaged)	.067	.052	0.064	0.052	0.053	0.065	0.065	0.055	0.110
(aged)	.059	.057	0.076	0.069	0.064	0.081	0.074	0.140	0.082
Swell ratio	3.9	3.3	3.7	2.5	2.6	2.6	2.8	2.4	2.7

Wear rate(mg/million cycles)

(unaged)	14	0.8	5
(aged)		0.6	

CLAIMS:

1. A process for preparing a medical implant having an improved balance of wear properties and oxidation resistance comprising the steps of:

5 irradiating a preform of ultrahigh molecular weight polyethylene to form free radicals;

annealing the irradiated preform by heating in a substantially oxygen-free atmosphere at a temperature at or above the onset of melting temperature for a time sufficient to recombine substantially all of the free radicals and cross-link the ultrahigh molecular weight polyethylene;

10 cooling the cross-linked preform while maintaining a substantially oxygen-free atmosphere:

forming a medical implant from the cross-linked preform;

packaging the medical implant in an air-permeable package; and

sterilizing the packaged implant using non-irradiative methods.

15

2. The process of claim 1 wherein the irradiating step comprises irradiating the preform with gamma radiation at a dose of 0.5-10 Mrad.

20 3. The process of claim 1 wherein the irradiating step comprises irradiating the preform with gamma radiation at a dose of 1.5-6 Mrad.

4. The process of claims 2 or 3 wherein the preform is contained in an inert atmosphere or vacuum during the irradiating step.

25 5. The process of claim 1 wherein the implant is sterilized using a gas plasma.

6. The process of claim 1 wherein the implant is sterilized using ethylene oxide.

30

7. The process of claim 1 wherein the annealing step is performed near or above the peak melting temperature.

8. The process of claim 1 wherein the annealing step is performed at a temperature greater than about 120°C.
- 5 9. The process of claim 1, wherein the annealing step is performed at a temperature of 120-170°C for 12-60 hours.
- 10 10. The process of claim 1 wherein the annealing step is performed for a time sufficient to form a cross-linked preform having an oxidation level of less than 0.2 carbonyl area/mil sample thickness after aging the cross-linked preform at 70°C for 14 days in oxygen at a pressure of about 5 atmospheres.
- 15 11. The process of claim 8 wherein the preform is irradiated with a dose of 1.5-6 Mrads and the irradiated preform is annealed at a temperature of 150-170°C for a period of 12-60 hours.
- 20 12. The process of claim 1 wherein the annealing step comprises melting the irradiated preform and applying an isostatic or hydrostatic pressure of 33-70 kpsi.
- 25 13. The process of claim 1 further comprising pre-annealing the preform at a temperature of 280°C - 355°C in an inert atmosphere without the application of external pressure for at least 0.5 hour prior to the irradiating step.
14. The process of claim 13 wherein the preform is pre-annealed at a temperature of about 320-355°C for at least 3 hours.
- 30 15. A process for preparing a medical implant having an improved balance of wear properties and oxidation resistance comprising the steps of:
irradiating a preform of ultrahigh molecular weight polyethylene to form free radicals;

annealing the irradiated preform by heating in a substantially oxygen-free atmosphere at a temperature at or above the onset of melting temperature to cross-link the ultrahigh molecular weight polyethylene;

cooling the cross-linked preform while maintaining a substantially oxygen-free atmosphere; and

5 forming a medical implant from the cross-linked preform.

16. The process of claim 15 wherein the irradiating step comprises irradiating the preform with gamma radiation at a dose of 0.5-10 Mrad.

10

17. The process of claim 15 wherein the irradiating step comprises irradiating the preform with gamma radiation at a dose of 1.5-6 Mrad.

15

18. The process of claims 16 or 17 wherein the preform is contained in an inert atmosphere or vacuum during the irradiating step.

19. The process of claim 15 wherein the implant is sterilized using a gas plasma.

20

20. The process of claim 15 wherein the implant is sterilized using ethylene oxide.

21. The process of claim 15 wherein the annealing step is performed near or above the peak melting temperature.

25

22. The process of claim 15 wherein the annealing step is performed at a temperature greater than about 120°C.

30

23. The process of claim 15 wherein the annealing step is performed at a temperature of 120-170°C for 12-60 hours.

24. The process of claim 15 wherein the annealing step is performed for a time sufficient to form a cross-linked preform having an oxidation level of less than 0.2 carbonyl area/mil sample thickness after aging the cross-linked preform at 70°C for 14 days in oxygen at a pressure of about 5 atmospheres.

5

25. The process of claim 22 wherein the preform is irradiated with a dose of 1.5-6 Mrads and the irradiated preform is annealed at a temperature of 150-170°C for a period of 12-60 hours.

10

26. The process of claim 15 further comprising pre-annealing the preform at a temperature of 280°C - 355°C in an inert atmosphere without the application of external pressure for at least 0.5 hr prior to the irradiating step.

15

27. The process of claim 26 wherein the preform is pre-annealed at a temperature of about 320°C - 355°C for at least 3 hours.

28. The process of claim 15 wherein the annealing step comprises melting the irradiated preform and applying an isostatic or hydrostatic pressure of 33-70 kpsi.

20

29. The process of claim 15 wherein the annealing step comprises melting the preform at a temperature of 280 - 355°C.

30. The process of claim 29 wherein the annealing step comprises melting the preform at a temperature of 320 - 355°C.

25

31. A medical implant prepared according to the process of claims 1 or 15.

32. A cross-linked ultrahigh molecular weight polyethylene having a swell ratio of less than about 5 and an oxidation level of less than about 0.2 carbonyl area/mil sample thickness after aging the ultrahigh molecular weight polyethylene at 70°C for 14 days in oxygen at a pressure of about 5 atmospheres.

33. The cross-linked ultrahigh molecular weight polyethylene of claim 31 having an oxidation level of less than about 0.1 carbonyl area/mil sample thickness after aging the ultrahigh molecular weight polyethylene at 70°C for 14 days in oxygen at a pressure of about 5 atmospheres.

5

34. A medical implant comprising the ultrahigh molecular weight polyethylene of claims 31 or 32.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/17776

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61L27/00 A61L31/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>PATENT ABSTRACTS OF JAPAN vol. 097, no. 009, 30 September 1997 & JP 09 122222 A (KYOCERA CORP). 13 May 1997, see abstract</p> <p>---</p> <p>WO 97 29793 A (MASSACHUSETTS INST TECHNOLOGY ;GEN HOSPITAL CORP (US)) 21 August 1997</p> <p>see page 6, line 1 - line 5 see page 7, line 12 - line 23 see page 12, line 7 - page 13, line 16 see page 14, line 2 - line 13 see page 17, line 1 - line 11 see claims 36-38,71,76,79,117</p> <p>---</p> <p>-/--</p>	1-3,7-9, 15-17, 21-23,31
P, X		1-4,7-9, 11, 15-18, 21-23, 25,29,31

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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1

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 729 981 A (BMG INC) 4 September 1996	1-4, 7-9, 11, 15-18, 21-23, 25, 31
Y	see page 3, line 26 - page 4, line 2 see page 4, line 31 - line 36 see page 8, line 1 - line 9 ---	6, 20
Y	EP 0 169 259 A (SURGICAL PATENT PRODUCTS INC LTD) 29 January 1986 see page 7, line 10 - line 25 see examples 1, 2 -----	6, 20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/17776

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